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RESPONSE TO PARENTERAL GLUCOSE OF NORMAL KIDNEYS AND OF KIDNEYS OF POSTOPERATIVE PATIENTS*†

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THE INADVISABILITY OF INFILCTING HEAVY LOADS of sodium chloride upon the early postoperative patient has been pointed out in previous reports.^{1, 2} Those studies were based upon data derived from patients undergoing combined abdominoperineal resection of the rectum, who were given infusions of various salt solutions. A definite variation from the normal handling of the infused salt loads was demonstrated for these patients. It is the purpose of this report to present similar studies using infusions of 5 per cent glucose, in an effort to further clarify the problems connected with the proper hydration of the early postoperative patient.

Data are presented of the urinary response to small positive loads of parenteral 5 per cent glucose, 1 to 1.5 per cent of body weight, in normal men and in patients following operations of varying magnitude. Infusion studies were carried out in three healthy young men, four patients undergoing herniorrhaphy and five patients undergoing combined abdominoperineal resection for carcinoma of the rectum. Rates of excretion of sodium, chloride, potassium and water, and velocity constants of water were calculated for each of the three groups of subjects.

PLAN OF STUDY AND PROCEDURE

The nine patients and three control subjects were unselected. However, they presented no evidence of gross cardiovascular and kidney disease. The patients undergoing combined abdominoperineal resection were prepared for operation by sulfasuxidine, and a high protein, high carbohydrate, low residue diet. They were transfused before operation when necessary to bring the hemoglobin to 14 Gm. per cent. The preanesthetic medication was morphine in combination with a barbiturate. The operations, with a single exception, were performed under spinal anesthesia, using nupercaine or continuous procaine. Ether was employed in one instance.

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All fluid was administered by the intravenous route, in volumes of 750 ml. at the rate of 6 ml./min. every six hours for four or five periods. The three controls received the infusions at the same rate and at the same clock times as the patients. No anesthesia was given in the case of the controls. The methods and procedures followed were those outlined in detail in the earlier paper.² *

RESULTS

A representative subject from each group, that is, one control, one from the herniorrhaphy group, and one of the combined resections was chosen for the presentation and comparison of complete data in Tables I and II. For convenience these groups in the above order will be referred to hereafter as Groups I, II and III.

TABLE I.—*Blood and Serum Changes in Parenteral 5 Per Cent Glucose*

Subject	Whole Blood			Serum				
	Specific Gravity	Hemo-globin Gm. %	Hema-tocrit Vol. %	Specific Gravity	Protein Gm. %	CO ₂ mM/L	Na mM/L	Cl mM/L
To.—Male control, age 22 yrs., 70.8 kg. 3000 ml. 5% glucose in 24 hours	(1) 1.0578 (2) 1.0581	15.7 16.6	45.3 53.0	1.0256 1.0265	6.21 6.52	25.2 25.8	138.9 139.1	104.3 98.5
Hu.—Female, herniorrhaphy, age 41 yrs., 70.5 kg. 3750 ml. 5% glucose in 30 hours	(1) 1.0531 (2) 1.0551	14.1 14.2	45.0 48.6	1.0221 1.0243	5.00 5.76	26.8 26.6	138.0 134.8	105.3 101.0
Bi.—Female, combined abdominal-perineal resection, age 69 yrs., 49.6 kg. 3750 ml. 5% glucose in 30 hours	(1) 1.0524 (2) 1.0506	13.0 12.5	41.5 42.4	1.0257 1.0240	6.24 5.66	25.8 25.4	134.9 123.0	102.8 94.0

(1) Before infusion and/or operation.

(2) At end of infusion period.

The whole blood and serum changes for these representative subjects are shown in Table I in which the preoperative and post-infusion findings are compared. It is interesting to note that in the control subject each post-infusion determination with the exception of the serum chloride revealed either an increased concentration of the constituent being measured, or, as in the case of the specific gravity, an indication of increased density of the entire blood sample. Although these changes are minimal they serve to indicate a

* Urines collected during each six-hour period were preserved by addition of 1 ml. of 12.8 per cent Zephiran and kept in the refrigerator. They were analyzed for pH, Na, K, NH₃, PO₄, SO₄, titratable acidity to pH 7.4, Cl, total nitrogen, urea nitrogen and creatinine. In one patient urinary calcium³ and magnesium⁴ were also determined. Losses of both elements were exceedingly small, amounting to approximately 1 milliequivalent per 24 hours.

Two blood samples, one under oil and one with heparin, were withdrawn before operation and at the end of the infusion period. Hemoglobin, volume of red cells, and whole blood specific gravity were determined in the heparinized samples; CO₂, Na, Cl and serum proteins in the serum.

general tendency, in that they are uniformly in the same direction. They are perhaps more indicative when compared to the subject from Group III. Here all the changes are in the opposite direction with the exception of the hematocrit, which shows little change. The figures for the patient undergoing herniorrhaphy seem to fall midway between Groups I and III. It thus appears that there is a tendency toward hemoconcentration in Group I and hemodilution in Group III with Group II showing little change.

The detailed urinary findings on these same three individuals are presented in Table II. The findings in the control subject appear to be typical

TABLE II.—*Composition of Urine, mEq. Per Liter*

Period	Vol. ml.	pH	Specific Grav- ity						Tit. Acid mEq.	Tot. N Gm/L	Urea N Gm/L	Creati- nine Gm/L	
			K mEq.	Na mEq.	NH ₃ mEq.	Cl mEq.	SO ₄ mEq.	PO ₄ mEq.					
Control To, Male—weight loss: 1.50 kg.													
Urine in bladder	5.95	1.009	48.0	91.0	24.7	90.3	41.3	28.5	22.6	10.407	9.301	1.250	
0-6th hr.	938	6.09	1.006	29.1	44.2	9.3	59.4	10.2	9.7	8.6	4.538	3.994	0.600
6-12th hr.	1120	6.58	1.005	8.8	37.4	6.5	34.8	6.3	6.9	3.4	2.519	2.100	0.388
12-18th hr.	590	5.95	1.004	18.9	10.7	11.6	15.5	6.2	10.7	12.4	4.180	3.484	0.750
18-24th hr.	500	6.03	1.003	18.9	4.4	12.4	6.3	5.5	11.6	13.2	4.123	3.416	0.913
Patient Hu, Female, herniorrhaphy—weight loss: 1.25 kg.													
12 ^o preop.	1315	6.61	1.009	44.9	109.8	11.1	99.5	25.4	19.5	14.1	5.714	4.997	0.739
0-6th hr.	530	7.02	1.004	31.3	47.9	6.8	49.0	7.1	14.2	6.0	2.969	2.454	0.491
6-12th hr.	299	7.37	1.004	36.2	63.5	7.9	45.8	11.4	15.8	5.0	3.697	3.409	0.729
12-18th hr.	415	5.52	1.005	32.4	11.1	19.5	14.0	12.9	26.6	54.1	4.090	3.515	0.845
18-24th hr.	840	5.93	1.002	13.7	6.5	8.1	12.3	6.2	7.5	17.5	2.885	2.658	0.420
24-30th hr.	1145	6.38	1.001	9.0	8.9	1.5	8.1	3.3	6.1	9.2	1.849	1.554	0.289
Patient Bi, Female, combined abdominoperineal resection													
12 ^o preop.	800	5.52	1.007	33.0	97.4	9.4	140.8	24.1	5.502	4.261	0.547
0-6th hr.	100	5.35	1.016	96.1	56.8	17.1	114.3	23.2	38.7	24.9	5.836	3.947	0.982
6-12th hr.	140	5.28	1.020	79.9	11.8	11.7	38.0	28.8	42.9	7.170	5.786	1.061
12-18th hr.	65	5.48	1.019	73.4	0.7	54.4	24.5	42.7	80.1	13.423	10.465	2.722
18-24th hr.	380	6.05	1.002	11.3	0.8	12.0	8.4	7.2	19.0	15.4	3.974	3.401	0.579
24-30th hr.	542	6.10	1.001	7.2	1.2	10.9	6.5	3.9	9.4	23.2	2.334	1.805	0.347

of the expected water diuresis in a normal adult. The urine volume is excessive for the first two periods following which it rapidly diminishes as the water is conserved by the kidneys. Excretion of sodium and chloride is also relatively large in the first two periods, but apparently those ions are also conserved in the last 12 hours since their concentrations are diminished in spite of the much smaller urinary volume. It is further noted that the specific gravity of the urine continues to fall in spite of the decrease in urine volume. The 24-hour urine volume for this subject exceeded by 148 ml. the total infusion and he lost 1.5 kg. in weight.

Patients Hu and Bi are found to differ to a considerable extent from the control. The former experienced no diuresis until the fourth period and her largest output was found in the fifth period. Throughout the five periods, however, her urine volume totaled only 521 ml. less than the volume of the infused solution. She lost 1.25 kg. in body weight. Patient Bi could never be

said to have experienced any diuresis, the largest urine volume being only 42 ml. in excess of the smallest volume excreted by the control. This patient was oliguric throughout the first three periods studied, and her total urine volume for the study was 2523 ml. less than the volume of fluid infused.

The concentration of the sodium and chloride ions in the urine of patients Hu and Bi approximated closely those found for the controls. The actual output, however, of these ions, as well as the other urinary constituents in the table, expressed either in total quantity or in excretion rates per hour, varied greatly from the control as will be found in succeeding tables.

An interesting finding for patient Bi is the slight increase in the specific gravity of the urine during the periods of oliguria. These determinations of specific gravity for Bi were representative of this group of patients as well as of other similar groups studied (see Tables VI and VII). There were, how-

TABLE III.—*Parenteral 5 Per Cent Glucose Cumulative Data: Water, Potassium and Salt; Controls*

Controls	Period	Urine: Composition			Urine: Excretion Rate			Water Load*	1/Δt	Serum Composition	
		Water ml.	Potassium mM	Sodium mM	Chloride mM	Water ml/hr.	Potassium mM	Sodium mM	Chloride mM	Sodium mM	Chloride mM
										/ml.	/ml.
Th. Male	0-6th	1408	28.5	53.1	46.1	234.7	4.8	8.9	7.7	- 923	- 0.250
Age: 26 yrs.	6-12th	2148	34.9	92.5	74.7	123.3	1.1	6.6	4.8	- 1191	- 0.104
Wt. loss:	12-18th	2808	39.5	105.4	84.9	110.0	0.8	2.2	1.7	- 1384	- 0.080
1.76 kg.	18-24th	3528	45.7	110.6	95.6	120.0	1.0	0.9	1.8	- 1637	- 0.073
To. Male	0-6th	938	27.3	41.5	55.7	157.6	4.6	6.9	9.3	- 385	- 0.409
Age: 22 yrs.	6-12th	2058	37.2	83.4	94.7	186.7	1.7	7.0	6.5	- 976	- 0.191
Wt. Loss:	12-18th	2648	48.3	89.7	103.9	98.3	1.9	1.1	1.5	- 1043	- 0.094
1.5 kg.	18-24th	3148	57.7	91.9	107.1	83.3	1.6	0.4	0.5	- 1028	- 0.081
Ta. Male	0-6th	610	19.7	25.0	39.1	101.7	3.3	4.2	6.5	- 88	- 1.155
Age: 24 yrs.	6-12th	1406	27.0	59.6	70.8	132.7	1.2	5.8	5.3	- 397	- 0.334
Wt. Loss:	12-18th	1891	34.8	69.2	83.1	80.8	1.3	1.6	2.1	- 370	- 0.218
0.59 kg.	18-24th	2359	40.4	73.5	90.7	78.0	0.9	0.7	1.3	- 346	- 0.225
										0.139	0.098

* Water load corrected for insensible loss and oxidative gain, estimated from glucose infused and urinary nitrogen.

ever, two patients (He and Sch, Table V) whose urinary specific gravity findings varied distinctly from the majority. These two patients revealed urinary specific gravities ranging between 1.028 and 1.035 throughout the entire study and the possibility of pre-existing and/or continuing dehydration was considered. In other data to be presented (Table V) further variations in the urinary excretion of these two patients are noted as compared to the other patients in Group III. It is of some interest that He and Sch are comparatively young men in contrast to the three elderly women who underwent similar operative procedures.

The individual cumulative data of urinary composition and the excretory rates for water, potassium, sodium and chloride for all subjects are contained

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in Tables III, IV and V. The calculated water load was corrected for insensible loss, oxidative gain from glucose combusted and water freed from destroyed tissue.*

TABLE IV.—*Parenteral 5 Per Cent Glucose Cumulative Data: Water, Potassium and Salt; Herniorrhaphy*

Patient	Period nr.	Urine: Composition			Urine: Excretion Rate			Water Load*	1/Δt	Serum Composition		
		Water ml.	Potas- sium mM	Sodi- um mM	Chlo- ride mM	Potas- sium Water ml/hr				Sodi- um mM /ml	Chlo- ride mM /ml	
						Water ml/hr	mM /hr	mM /hr				
Do. Male	0-6th	192	7.3	26.4	23.3	32.0	1.2	4.4	3.9	217	0.148	
Age: 46 yrs.	6-12th	446	22.4	62.7	56.2	42.3	2.5	6.1	5.5	449	0.094	
77.3 kg.	12-18th	984	41.7	102.0	101.1	89.7	3.2	6.6	7.5	419	0.214	
	18-24th	1904	54.1	130.8	133.7	154.0	2.1	4.8	5.4	-18	-9.111	
	24-30th	2706	67.5	159.1	164.5	133.7	2.2	4.1	5.1	-337	-0.397	
Ho. Male	0-6th	229	21.2	43.8	54.0	49.5	3.5	7.3	9.0	297	0.167	
Age: 54 yrs.	6-12th	504	31.3	84.8	97.4	45.8	1.7	6.8	7.2	526	0.087	
70 kg	12-18th	909	48.0	120.5	142.2	67.5	2.8	6.0	7.5	634	0.107	
Wt. Loss:	18-24th	1152	62.5	133.1	166.4	40.5	2.4	2.1	4.0	892	0.045	
1.6 kg.	24-30th	1787	69.8	144.5	183.8	105.8	1.2	1.2	2.9	746	0.142	
Hy. Male	0-6th	168	11.1	12.9	22.2	28.0	1.9	2.2	3.7	396	0.071	
Age: 63 yrs.	6-12th	286	20.1	21.9	36.9	19.7	1.5	1.5	2.5	831	0.024	
56 kg	12-18th	866	32.6	34.6	57.6	96.7	2.1	2.1	3.5	828	0.117	
	18-24th	2181	40.7	49.1	78.5	219.2	1.4	2.4	3.5	81	2.706	
	24-30th	3145	47.9	60.3	93.9	160.7	1.2	1.9	2.6	-191	-0.841	
Hu. Female	0-6th	530	16.9	25.4	25.5	88.3	2.8	4.2	4.3	-39	-2.260	
Age: 41 yrs.	6-12th	829	27.7	44.4	39.2	49.8	1.8	3.2	2.3	145	0.343	
70.5 kg.	12-18th	1244	41.2	49.0	45.0	69.2	2.3	0.8	1.0	224	0.309	
Wt. Loss:	18-24th	2064	52.7	54.4	55.3	140.0	1.9	0.9	1.7	-110	-1.273	
1.3 kg.	24-30th	3209	63.1	64.6	64.6	190.8	1.7	1.7	1.6	-775	-0.253	
											0.136	
											0.101	

* Water load corrected for insensible loss and oxidative gain, estimated from infused glucose and urinary nitrogen.

The concentrations of sodium and chloride in the serum, before and at the conclusion of the infusion periods, are included in these tables to emphasize once again the variation in the three groups. A tendency toward equal pre- and post-infusion levels is found in Group I. There is a definite trend, however, in Group III toward a decreased concentration of these ions in the post-infusion samples.

* The water freed by tissue destruction was estimated from urinary nitrogen by use of the factor 6.25, the water gained equalling 0.27 liters per 100 Gm. protein.⁵ Insensible loss was estimated as 0.07 per cent of body weight per hour.⁶ Thus the total water load equalled the infused fluid, plus water freed by combustion of glucose and destruction of tissue, minus urinary water and insensible loss.

The velocity constants for water excretion are also included in these tables. These are calculated (after the method of Wolf⁷) by dividing the average rate of excretion during the six-hour period by the load at the end of the period.

TABLE V.—*Parenteral 5 Per Cent Glucose Cumulative Data: Water, Potassium and Salt; Combined Abdominoperineal Resections*

Patient	Period hr.	Urine: Composition			Urine: Excretion Rate			Water Load*	1/Δt	Serum Composition				
		Potas- sium ml.		Sodi- um mM	Chlo- ride mM	Potas- sium Water ml/hr	So- dium mM /hr	Chlo- ride mM /hr		Sodi- um mM /ml	Chlo- ride mM /ml			
He	Male	0-6th	50	5.9	4.7	6.0	8.3	1.0	0.8	1.0	426	0.020	0.136	0.102
Age: 23 yrs.		6-12th	133	19.2	8.8	15.1	13.8	2.2	0.7	1.5	823	0.017		
70 kg.		12-18th	293	51.5	15.1	29.8	26.7	5.4	1.1	2.5	1165	0.023		
		18-24th	563	87.5	29.8	48.1	45.0	6.0	2.5	3.1	1424	0.032		
		24-30th	877	123.2	57.2	67.1	52.3	6.0	4.6	3.2	1650	0.032	0.123	0.091
Sch	Male	0-6th	417	10.4	20.6	16.0	69.3	1.7	3.6	2.7	48	1.440	0.134	0.099
Age: 41 yrs.		6-12th	687	55.1	47.4	27.0	45.0	7.5	4.5	1.8	158	0.285		
79.5 kg.		12-18th	905	90.3	74.2	35.4	36.3	5.7	4.5	1.4	410	0.089		
		18-24th	1088	118.5	96.9	43.8	30.5	4.8	3.8	1.4	596	0.051		
		24-30th	1373	147.5	117.1	56.5	47.5	4.8	3.4	2.1	806	0.059	0.121	0.092
Ro	Female	0-6th	64	5.6	6.1	7.5	10.7	0.9	1.0	1.3	445	0.024	0.133	0.107
Age: 56 yrs.		6-12th	234	22.3	21.0	23.5	28.3	2.8	2.5	2.7	798	0.036		
61.4 kg.		12-18th	406	34.5	24.9	31.6	28.7	2.0	0.7	1.4	1151	0.025		
		18-24th	1266	44.4	27.9	38.5	143.3	1.7	0.5	1.2	818	0.175		
		24-30th	1898	53.8	31.8	48.9	105.3	1.6	0.7	1.7	717	0.147	0.130	0.097
Cu	Female**	0-6th	200	5.2	10.6	12.4	33.3	0.9	1.8	2.1	312	0.107	0.139	0.111
Age: 53 yrs.		6-12th	405	12.5	14.1	19.7	34.2	1.2	0.6	1.2	626	0.055		
61.6 kg.		12-18th	575	19.3	16.1	28.0	28.3	1.1	0.3	1.4	953	0.030		
Wt. gained:		18-24th	715	23.8	17.8	37.9	23.3	0.8	0.3	1.7	1340	0.017		
0.7 kg.		24-30th	907	30.6	19.9	52.4	32.0	1.1	0.4	2.4	1672	0.019	0.134	0.097
Bi	Female	0-6th	100	9.6	5.7	11.4	16.7	1.6	1.0	1.9	463	0.036	0.135	0.103
Age: 69 yrs.		6-12th	240	20.7	7.4	16.7	23.3	1.9	0.3	0.9	892	0.026		
49.6 kg.		12-18th	305	25.5	7.5	18.3	10.8	0.8	0.0	0.3	1395	0.008		
		18-24th	685	29.8	7.8	21.5	63.3	0.7	0.1	0.5	1594	0.040		
		24-30th	1227	33.7	8.5	25.0	90.3	0.7	0.1	0.6	1627	0.056	0.123	0.094

* Water load corrected for insensible loss and oxidative gain, estimated from glucose infused and urinary nitrogen.

** Ether anesthesia, colostomy, inoperable carcinoma of rectosigmoid.

For clearer visualization of the variations demonstrated by these three groups of patients in the handling of the infusions, postoperative rates of urinary excretion for each group have been averaged and compared graphically in Figure 1. Although the averages in each instance include a relatively small series of cases, the trends for each group seem quite definite.

The rates of urinary excretion for water, sodium and chloride are illustrated in Sections A and B. The diuresis is again noted for the control group in the first two infusion periods. This is accompanied by a relatively high excretion rate of sodium and chloride until the third and fourth periods at which time both sodium and chloride are more adequately conserved. The Group III patients, on the other hand, reveal very low excretion rates of water and salt throughout the entire study. The highest rate of water excretion, as attained in the fourth and fifth periods, was less than two-thirds the

lowest value recorded for the controls. The excretion rate of sodium represented a flat curve throughout the entire study. The course of the herniorrhaphy group was again found midway between Groups I and III. These patients followed an initial 12-hour oliguria with a pronounced diuresis in the last two to three periods. The rate of sodium excretion, however, was greater during the oliguria than it was during the last two periods when very dilute urine was being excreted.

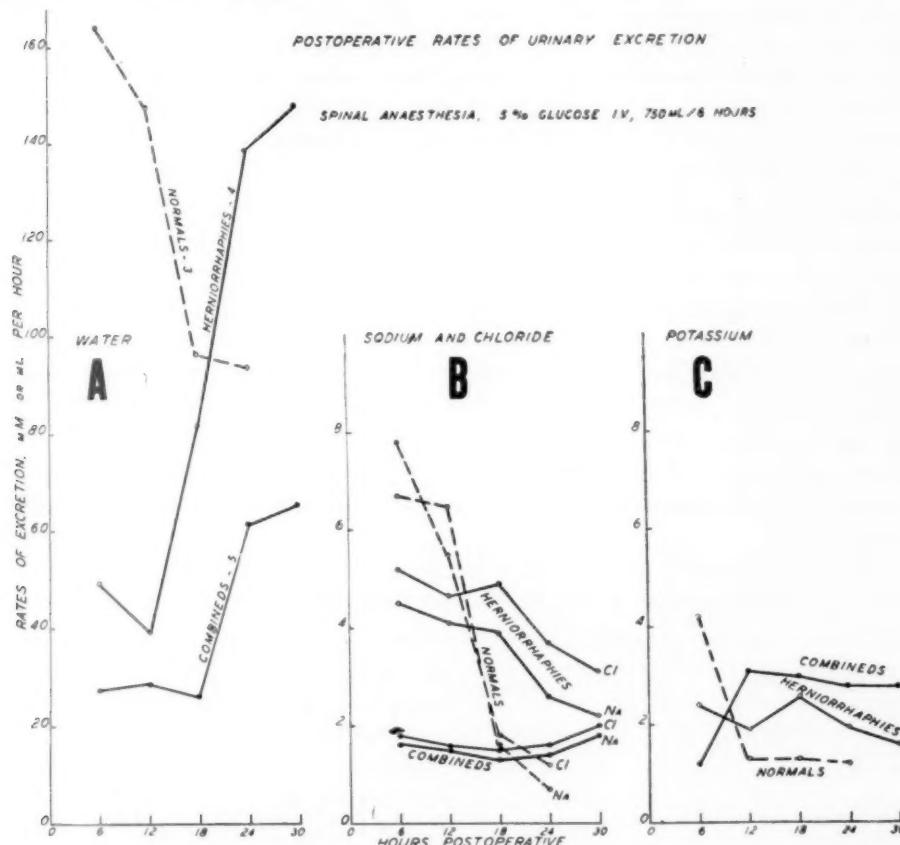


FIG. 1.—Average postoperative rates of urinary excretion of water, sodium, chloride and potassium plotted against time for normal men (3), patients undergoing herniorrhaphy (4) and combined abdominoperineal resection (5).

The urinary excretion rates of potassium for these patients are found in Section C. This factor, however interesting, is being discussed independently in another communication.

DISCUSSION OF RESULTS

Infusions of 5 per cent glucose given in the dosages described above are apparently handled differently by each of the three groups of patients studied. The solution produced dehydration uniformly in the control subjects as a

result of an initial diuresis and salt loss not completely compensated during the 24 hour study. The tendency in the herniorrhaphy group was toward only slight dehydration, the diuresis occurring after 12 to 18 hours and being simultaneous with a decreased rate of sodium excretion. The excretion of both water and salt remained low throughout the study of patients undergoing combined abdominoperineal resection of the rectum. This resulted in a positive water load at the conclusion of the study on these patients. The most striking contrast in urinary output between the control group and the two operated groups occurred in the first six postoperative hours.

Two interesting questions are posed by the above results: (1) What are the reasons for the variations in the handling of these infusions by the three groups studied, and (2) what is the clinical significance?

No single answer to the first question would seem possible when one considers all the possibilities and complexities involved. It does seem reasonable, however, to rule out some of the more obvious explanations by means of additional data acquired in further investigations.

The initial oliguria, most pronounced in the Group III patients, makes necessary the consideration of possible preoperative dehydration as a causative factor. Certainly the hydration previous to these studies could not be absolutely controlled. All patients, however, were able to take adequate nutrition by mouth preoperatively and were felt clinically to be optimally prepared for their surgical procedures. Furthermore, the control group as well as the two operated groups was deprived of all food and fluid for 12 hours before the study.

It would appear from Figure 1, Sections A and B, that the more extensive the operation, the more severe and prolonged is the immediate postoperative oliguria. It might thus be postulated that the oliguria is a result of excessive fluid losses at operation, such as operative hemorrhage or fluid lost into the wound. Further operative losses would include the possibility of a greater insensible water loss during the procedures of greater magnitude, or increased loss through perspiration. No allowance was made for these factors in the water loads calculated. In considering either preoperative or operative dehydration as factors influencing the oliguria found in these patients, reference is again made to the determinations of urinary specific gravity. If a high urinary specific gravity can be used as an index of dehydration, only two of the Group III patients (He and Sch) may be considered as dehydrated on this basis.

To explore the possibility of dehydration more thoroughly, some data were collected on two further groups of patients. In one group of six patients undergoing combined abdominoperineal resection of the rectum (Group IV), blood transfusions were given in the first six postoperative hours in addition to the 750 ml. of 5 per cent glucose as given previously. The blood was given during the operation, usually as a prophylactic measure, and in the amounts calculated by the operating surgeon as adequate replacement for the blood lost. The infusions in Group IV, therefore, differed from those in Group

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III only in that blood losses were adequately replaced in the former. The oligurias demonstrated in the first six postoperative hours (Table VI) and the specific gravities of the urines for these two groups are similar in spite of the variation in blood administered.

TABLE VI.—*Parenteral 5 Per Cent Glucose and Blood Intake, Output and Urinary Specific Gravity; Combined Abdominoperineal Resections*

Patient	Hours Postop.	Intake in ml.		Output in ml.	
		Blood	5% Glucose	Urine	Specific Gravity
Ra	0-6	400	750	125	1.015
Male	6-24	2250	235	1.011
61 yrs.	24-30	750	72	1.012
We	0-6	900	750	123	1.013
Male	6-24	2250	535	1.008
47 yrs.	24-30	750	550	1.005
Wa	0-6	900	750	100	1.022
Male	6-24	2250	1205	1.019
70 yrs.	24-30	750	515	1.005
Gr	0-6	1000	750	125
Female	6-24	2250	1435	1.003
20 yrs.	24-30	750	290	1.007
My	0-6	500	750	85	1.022
Male	6-24	2250	515	1.018
54 yrs.	24-30	750	95
Fi	0-6	500	750	145	1.013
Male	6-24	2250	360
60 yrs.	24-30	250	580	1.005

In a fifth group (Group V) the urinary output was carefully recorded, but the fluid intake was left to the discretion of the staff in charge. These patients received their required blood transfusions and fluid infusions in one continuous drip, which was started during the operation and was completed within five to eight hours. The intakes and outputs for these patients are found in Table VII.

The infusions for the patients in Group V differed from those in Group III not only in that adequate blood replacement was administered but also as to injection times. Consequently, large volumes of fluid were administered during the period of oliguria. The urine volumes, however, were again found to be small in the first six postoperative hours. Patient La, for example, received an infusion totalling 3800 ml. in the first six hours, and his total urine volume for that period was 55 ml. with a specific gravity of 1.008. Whether or not the oliguria found in these patients in the first six hours postoperatively is caused by preoperative or operative dehydration, it can be stated that it is not altered by adequate blood replacement or rapid, massive infusions of fluid.

The anesthetic agent as a contributing cause cannot be ruled out. Although

the majority of the patients studied received a continuous spinal anesthesia, using procaine as the anesthetic agent, it was found that the results were not changed by varying the type of anesthetic employed. Some of the modifications of anesthesia included sodium pentothal as a supplement to the spinal, nitrous oxide-oxygen-ether general anesthesia, and cyclopropane with curare. Previous studies on renal function under anesthesia⁸ have revealed no change in glomerular filtration rate or renal blood flow under the above three anesthetics if the factor of hypotension could be eliminated. It might be noted that the patients undergoing herniorrhaphy in Group II also received procaine spinal anesthesia, although, of course, in a more limited quantity.

TABLE VII.—*Early, Continuous Parenteral Infusions Plus Blood Intake, Output and Urinary Specific Gravity; Combined Abdominoperineal Resections*

Patient	Intake in ml.					Output in ml.			Comment
	Hours	5%	Blood	Glucose	Saline	Hours	Urine	Specific Gravity	
	Postop.					Postop.			
Bo 67 yrs.	0-8	1500	3000	250	0-6	210		
						6-24	380	1.018	
						24-30	45		
Ki 56 yrs.	0-8	1000	2600	850	0-9	350	1.015	Ether and curare anesthesia. Shock.
						9-25	390		
Ge 63 yrs.	0-7	3000	0-6	250		
						6-24	610		
Ka 49 yrs.	0-6	3000	0-8	191	Shock at 12 hours postoperatively.
	12-15	500	400	8-24	705	
La 71 yrs.	0-6	1000	2000	800	0-6	55	1.008	Ether anesthesia.
						6-24	1305	1.014	
Da 52 yrs.	0-7	1000	1000	600	200	0-24	1100	Sigmoid resection.
Pi 40 yrs.	0-9	1000	1100	1000	1400	0-24	675	Laparotomy and biopsy, cyclopropane and curare anesthesia.

The factors of hypotension, shock and cellular anoxia must be considered in evaluating these results. The anesthetic records of all these patients have been carefully studied and only two of them (Ki and Ka) developed the syndrome indicative of surgical shock. Even those patients who received no transfusions remained free from this complication—in fact, had shock developed in one of the latter patients he would have been automatically eliminated from this category, for no transfusions were withheld if the condition of

the patient indicated the need. It cannot be stated, however, that none of these patients showed any transient periods of hypotension, as the majority did develop this complication for a brief interval at some time during the course of the operation. This was usually felt to be a result of the spinal anesthesia and responded well in all instances to one of the vaso-pressor drugs. Although no clinical signs of shock or anoxia developed in these patients, it is of course impossible to obtain any estimation of the amount of compensatory vaso-constriction which may have been present even though the full-blown clinical picture of shock was not evident. Once again, however, it is of interest to note that the results in patients with and without blood replacement were similar.

In attempting to evaluate the degree of clinical significance which might be attached to the data presented, reference may well be made to the average water loads and sodium losses in the original three groups of patients. The average water load, for example, in the control group over the 24 hour study period was — 1003 ml., accompanied by an average sodium loss of 92 mEq. Although this is a loss of water slightly in excess of sodium (as compared to the concentration of extracellular fluid), the excess is not large and is further minimized by the renal conservation of sodium, as shown in the last period when an average of only 3.6 mEq. of sodium were excreted in the urine. A salt water deficit is thus present in the control group but is being controlled adequately by normal renal function, even though absolute salt conservation cannot be expected.

The average water load in the herniorrhaphy group over the 30 hour study period is found to be — 139 ml., with an average sodium loss over the same period of 107 mEq. These patients then have lost salt in excess of water. This change involves less than one liter of extracellular fluid during the first 30 postoperative hours and is being well compensated in the last study period at which time water is being excreted in excess of sodium (887 ml. of water and 15.3 mEq. of sodium). In this group, then, there is small but definite derangement of body fluids in the first 12 postoperative hours, which is held in check when compensation is begun through more adequate renal function in the last two periods.

In the patients undergoing combined abdominoperineal resection, a positive water load averaging 1300 ml. is found for the first time at the end of the 30-hour study period. At the same time the sodium loss, though minimal, is present and averages 47.3 mEq. over the 30 hour period. Here, then, is the only group whose averages reveal a positive water load with a negative sodium load. Renal compensation in the latter part of the study which was evident in the first two groups is minimal for these patients as noted by the curves in Figure 1, Sections A and B. It is further noted that small amounts of sodium excreted by these patients throughout the first two postoperative periods are apparently not the result of renal conservation of salt, but rather a function of the small quantities of urine produced, for, as shown in Table II, the concentration of salt in the urine of one of these patients closely approxi-

mated that of the representatives of the other two groups. The pre- and post-infusion blood studies in Table I confirm the results of these urinary analyses.

It would appear, then, that the administration of 5 per cent glucose solution in the quantities employed in this study should be free of serious derangement of body fluids in normal, healthy persons and in healthy individuals undergoing operations of the magnitude of herniorrhaphy.

In patients undergoing combined abdominoperineal resection of the rectum, renal excretion of both salt and water is apparently quite different from the normal, with urinary volumes greatly depressed in the first six to twelve post-operative hours. The result is a positive load of water accompanied by a small urinary loss of salt; at the same time, evidence of hemodilution is encountered in the blood. These findings appear to be independent of the load of 5 per cent glucose administered and of the rate of administration, and are not affected by the replacement of the blood loss during operation.

It would seem to follow that the administration of intravenous infusions of 5 per cent glucose in these patients should not be "pushed" during the first hours postoperatively, in spite of low urinary output. The practice of starting an intravenous infusion before operation and continuing this infusion at a relatively rapid rate until a 24 hour supply of water has been injected into the patient within the first six to eight postoperative hours seems unjustified. Although frequently no ill effects from this procedure are observed, its practice in the malnourished, chronically ill, elderly patient certainly should increase the danger of such complications as pulmonary edema, wound edema, cardiac failure and water intoxication.

Careful planning in the prescription of 5 per cent glucose infusions in these patients in the immediate postoperative period is as important as in the prescription of saline infusions. The giving of sufficient 5 per cent glucose during this period (6-12 hours) to cover the calculated insensible water loss in addition to transfusions of blood to replace adequately the blood lost would seem to be a logical handling of the situation. Further infusions after the first 12 hours could then be given in amounts calculated for adequate renal requirements.

SUMMARY

Infusions of 5 per cent glucose were administered to three control subjects, four patients undergoing herniorrhaphy and five patients undergoing combined abdominoperineal resection of the rectum. Each individual was given 750 ml. of 5 per cent glucose in each of four or five periods of six hours. Excretion rates and loads of water, sodium, chloride and potassium were determined.

The control group revealed an initial diuresis in the first six to twelve hours with accompanying losses of salt. In the third and fourth periods renal conservation brought the excretion of both water and salt to a minimum. The subjects were somewhat dehydrated at the conclusion of the study, as indicated by loss of weight and greater losses of water than salt.

The patients undergoing herniorrhaphy experienced, on the average, reduced excretions of water during the first two periods, which changed to a definite diuresis in the later periods. Sodium and chloride were excreted more rapidly during the periods of low water output, but were conserved during the diuresis. These patients lost, on the average, small amounts of salt in excess of water, but again adequate renal compensation was in evidence at the conclusion of the study.

Data from patients undergoing combined abdominoperineal resection of the rectum revealed an oliguria occurring in the first six to 12 postoperative hours, which was associated with minimal output of sodium and chloride throughout the study period. As a result, there was a positive load of water accompanied by a small loss of salt.

Some of the causative factors associated with these differences in the handling of 5 per cent glucose are discussed. Further data are presented which show that the addition of either adequate blood replacement during operation or infusions of large volumes of glucose in the early postoperative period are without influence upon the oligurias noted in those patients undergoing large operations.

During the first six to 12 hours after operation, it is recommended that intravenous infusions be limited to transfusions of blood to replace blood loss and to that amount of 5 per cent glucose required to replace insensible loss of water. After this period, and following a careful evaluation of the patient's state of hydration, sufficient 5 per cent glucose may be infused to support renal function adequately.

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APPRAISAL OF ORAL STREPTOMYCIN AS AN INTESTINAL ANTI-
SEPTIC, WITH OBSERVATIONS ON RAPID DEVELOPMENT
OF RESISTANCE OF *E. COLI* TO STREPTOMYCIN*

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THE ACTIVITY OF STREPTOMYCIN against gram negative organisms and its negligible absorption from the alimentary tract, as shown in the writings of Waksman and others,^{1, 2, 3, 4, 5} has prompted the oral administration of this antibiotic in an attempt to reduce the bacterial flora in the large bowel preparatory to surgery. It is the purpose of this paper to present an appraisal of the effectiveness of oral streptomycin in reducing the numbers of intestinal bacteria in preoperative cases, in the light of the experiences of this clinic and a review of the publications from other clinics.

Preliminary reports of the effectiveness of streptomycin in intestinal prophylaxis by Zintel⁶ were encouraging. In a series of 15 patients who were given 0.25 Gm. of streptomycin by mouth every six hours and followed with quantitative stool cultures, Zintel reported a marked and sustained reduction in the numbers of the three groups of organisms studied (coliform group, *streptococcus fecalis*, and clostridia). The patients in Zintel's series were followed from six to ten days after institution of streptomycin. A later paper⁷ reported essentially the same findings in greater detail.

Rowe, *et al.*⁸ studied the effects of oral streptomycin and sulfathaladine, singly and in combination, on the coliform group of organisms. These authors gave one group of patients oral streptomycin alone, a second group sulfathaladine, and a third group a combination of the two drugs. The dosage of streptomycin used was 2 Gm. daily. A marked reduction in the numbers of coliform organisms in most of the patients in this series was found to occur within 48 hours, but a reversion was noted in two patients following prolonged administration. These authors concluded that streptomycin should not be used longer than 72 hours preceding surgery.

Poth⁹ suggested that streptomycin given orally before surgery might produce deleterious effects by virtue of the marked reduction in the bacterial flora, particularly in the upper alimentary tract, thereby interfering with the absorption of certain fat soluble substances, most important being vitamin K, resulting in an elevated prothrombin time. Another valid objection offered by this author was that in view of the rapid resistance to streptomycin developed by the intestinal bacteria, one would be reducing the usefulness of the drug in the treatment of postoperative complications, should such develop.

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The observations of Paine and Finland¹⁰ on streptomycin resistant and dependent bacteria are pertinent in this connection. While our work was in progress these authors reported work along similar lines with various groups of organisms, including *E. Coli*. They report that strains of streptomycin-sensitive, streptomycin-resistant, and even streptomycin-dependent organisms appear after exposure to various concentrations of streptomycin.

A series of 24 cases receiving oral streptomycin alone and nine cases receiving streptomycin and sulfathaladine in combination have been studied with quantitative estimations being made of the changes in stool bacteria which occur during preoperative administration of these drugs. The cases reported were selected at random from among patients admitted to Presbyterian Hospital for large bowel lesions; the diagnoses included carcinoma of the rectum, carcinoma of the sigmoid, chronic ulcerative colitis, diverticulitis, polyposis, and fistula in ano (tuberculous and non tuberculous). In this series, the three major groups of alimentary tract organisms were studied, namely the coliform group, the intestinal streptococci, and the clostridia, by the method described below.

BACTERIOLOGIC TECHNIC

Stools were obtained for culture before and every one or two days after the institution of oral streptomycin. The cases were followed for periods ranging from five to 14 days after the institution of chemotherapy. An emulsion of 1 Gm. of fresh wet stool in 9 cc. of sterile broth was prepared in a glass plunger type homogenizer. This 1:10 dilution of the stool was then carried through a continued series of eight 1:10 dilutions so that the last was 10^{-8} /x the concentration of the original stool specimen. One-half cubic centimeter portions of tubes two, four, six and eight were used for inoculating agar plates of the following media:

- (1) Eosin methylene blue for coliform organisms. Surface lactose-fermenting colonies were counted after 24 hours incubation at 37° C.
- (2) Modified Wilson Blair for clostridia. Two-tenths cubic centimeter of 8 per cent Ferric Chloride and 2.0 cc. of 20 per cent sodium sulfite were added just before use to 20 cc. of liquid meat infusion agar. Pour plates were made, the colonies of clostridia appearing as black spots in the medium after 24 hours anaerobic incubation.
- (3) Two per cent Dextrose meat infusion agar, buffered with NaOH to pH 9.3 for streptococci. Pour plates were also made with this medium, the streptococci appearing as small millet seed shaped colonies in the medium, and colonies were counted after 72 hours incubation.

Colony counts were then made on the plate of highest dilution in which colonies appeared for each of the three groups of organisms. By this method a relatively accurate approximation of the total number of organisms in each stool was gained.

RESULTS AND INTERPRETATION

A total of 24 patients received oral streptomycin alone. 19 of whom received

0.25 Gm. every six hours, the other five receiving 1.0 Gm. every six hours. No essential difference in results obtained was noted in the two groups.

The effects of 0.25 Gm. of oral streptomycin upon the three classes of organisms studied in the group of 19 preoperative patients scheduled for large bowel surgery receiving the dosage are shown in the accompanying table (Table I). The discrepancy in the total number of patients upon whom counts were done for the three types of organisms is due to the fact that technical errors in preparing media rendered two streptococcus controls

TABLE I.—*Response of Colony Counts to 1.0 Gm. of Streptomycin Per Day*

Degree of Response	Number Giving No Response	Number Giving Temporary Response		Number Giving Prolonged Response		Total Number of Cases
		To 0.01%	To 0.001% or Less	To 0.01%	To 0.001% or Less	
<i>E. Coli</i>	9	1	4	1	4	19
Streptococcus	15	1	0	0	1	17
<i>Cl. welchii</i>	7	0	4	0	7	18

and one *Clostridium welchii* control unreliable. These and subsequent cultures on the same patients were therefore not included in the results tabulated.

The patients were grouped according to whether they gave (1) no significant response to the drug (*i.e.*, a drop to not less than 0.1 per cent of the original colony count), (2) a temporary response, and (3) a prolonged response. These two latter groups were subdivided into (a) those which dropped to 0.01 per cent of the original count and those which dropped to 0.001 per cent of the original count or less. To allow for the expected variation in the method no drop in colony count of less than to 0.01 per cent of the original count was considered significant in terms of clinical benefit to be derived although a drop to 0.1 per cent of the initial value is probably bacteriologically significant. In all instances in which the reduction in colony count was to 0.001 per cent of the original count or less, the remaining population was 200 organisms or less per gram of wet stool, this being the smallest number which could be counted by this technic.

Of the 19 patients receiving 1 Gm. of streptomycin per day, nine, or 47.7 per cent, showed no significant response in the *E. Coli* colony counts, and 10, or 52.3 per cent, showed a significant response. Of the latter group only five (26.1 per cent) remained at a lowered count for the duration of the preoperative period. In these five cases the last stool cultures were obtained five, seven, eight, 13, and 14 days after the institution of oral streptomycin. In all ten cases in which there was a significant drop in colony count, this had occurred by the second day in seven patients, by the third day in two, and by the fourth day in one patient. This would indicate that in those which do respond the maximum response is obtained by the second to the fourth day on this regimen, after which a large proportion of the responsive cases (50

per cent in this series) will show a rapid return to the original bacterial counts. (In the light of these observations an investigation of the development of resistance by various strains of *E. Coli* to streptomycin was undertaken. This will be discussed in more detail below.)

Among the 17 patients upon whom serial counts were done for streptococci, 15, or 87.7 per cent, showed no significant reduction in the number of organisms, one showed a temporary reduction, and one a prolonged reduction. This would suggest that very little reduction in streptococcal population may be expected by the oral administration of streptomycin.

Among the 18 patients in whom counts were carried out for clostridia, seven, or 38.9 per cent, showed no significant reduction in the total count; four, or 22.2 per cent, a temporary reduction, and seven, or 38.9 per cent, a prolonged reduction. The reduction in the number of clostridia present generally occurred more gradually than with the coliform group, when a drop did occur, the decline taking place between the second and the seventh day. The subsequent rise, when it occurred, took place within two to four days after the maximum reduction.

Five cases received 4 Gm. of streptomycin per day (1 Gm. every six hours). A tabulation of these figures (Table II) shows that there appears

TABLE II.—*Response of Colony Counts to 4.0 Gm. of Streptomycin Per Day*

Degree of Response	Number Giving No Response	Number Giving Temporary Response		Number Giving Prolonged Response		Total Number of Cases
		To 0.01%	To 0.001% or Less	To 0.01%	To 0.001% or Less	
<i>E. Coli</i>	3	0	0	0	2	5
Streptococcus	4	0	0	0	1	5
<i>Cl. welchii</i>	2	0	1	0	2	5

to be no significant difference between this small group of cases and those treated with 1 Gm. per day. Because of the rapid development of resistant strains of organisms and the lack of significant difference in results, the larger dosage was abandoned in our series of cases.

None of the toxic effects seen with the parenteral administration of streptomycin were observed in any of the series of cases. Prothrombin times were determined by the Quick method every two to four days in 11 patients in this series and in seven of them there appeared a slight prolongation. In no instance was this increase more than 4.5 seconds, 22 seconds being the highest prothrombin time recorded in this group (14 \pm 1 second being normal). No consistent correlation was found between a rise in prothrombin time and a drop in bacterial flora.

DEVELOPMENT OF RESISTANCE OF *E. COLI* TO STREPTOMYCIN

The rapid return to pre-treatment levels of bacterial counts in so many of our patients led to an investigation of the development of streptomycin

resistance by *E. Coli* in a group of ten cases chosen at random from this series.

Preliminary titrations had shown that in these patients the *E. Coli* isolated before administration of oral streptomycin were sensitive to and completely inhibited by 1.25 units of streptomycin per cubic centimeter. After treatment the organisms rapidly became resistant to at least 100 units/cc. Therefore a wide range was selected, *i.e.* 0 to 10,000 units/cc., distributed as in Figure 1.

STREPTOMYCIN RESISTANCE OF *E. COLI*

	UNITS/CC.	0	19	39	78	156	312	625	1250	2500	5000	10,000
LO.	0	+	0	0	0	0	0	0	0	0	0	0
	24	+	+	+	+	+	+	0	0	+	+	+
CO.	0	+	0	0	0	0	0	0	0	0	0	0
	24	+	+	+	+	+	+	0	0	+	+	+
BO.	0	+	0	0	0	0	0	0	0	0	0	0
	24	+	+	+	+	+	+	0	0	+	+	+
O'D.	0	+	0	0	0	0	0	0	0	0	0	0
	24	+	+	+	+	+	+	+	+	+	+	+
EP.	0	+	0	0	0	0	0	0	0	0	0	0
	24	+	+	+	+	+	+	0	0	+	+	+
TR.	0	+	0	0	0	0	0	0	0	0	0	0
	24	+	0	0	0	0	0	+	+	+	+	+
BR.	0	+	0	0	0	0	0	0	0	0	0	0
	24	+	+	+	+	+	+	0	0	+	+	0
CR.	0	+	+	+	+	+	0	0	0	+	+	+
	24	+	+	+	+	+	+	0	0	+	+	+
RI.	0	+	0	0	0	0	0	0	0	0	0	0
	24	+	+	+	+	+	+	0	0	+	0	+
PU.	0	+	0	0	0	0	0	0	0	0	0	0
	24	+	+	+	+	+	+	+	0	+	+	+
		+	+	+	+	+	+	+	+	+	+	+

+ INDICATES GROWTH AT GIVEN STREPTOMYCIN CONCENTRATION
0,2,4 INDICATES DAY OF THERAPY WHEN CULTURE WAS OBTAINED

FIG. 1

From each stool specimen the *E. Coli* were isolated in pure culture on EMB agar. An inoculum for titration was prepared by placing one loop of the organism into five cubic centimeters of streptomycin broth (a standard specified by the U.S.F.D.A.) and incubated at 37° C. for five hours. One drop of this inoculum was added to two cubic centimeters of the titration broth and incubated for 72 hours at 37° C. and read at the end of that time for visible turbidity.

The results revealed that prior to treatment the *E. Coli* were inhibited in all but one case by the lowest concentration of streptomycin used, *i.e.*, 19

units/cc. This one exception was resistant to 156 units/cc. After 48 hours of oral streptomycin, the organisms isolated were found to be resistant to at least 156 units/cc. in all but one case, this strain requiring six days for the development of resistance. In one case the organism grew in all the titration concentrations after 48 hours of oral streptomycin. This was observed on prolonged treatment in two other cases.

A marked prozone phenomenon was observed in these titrations. In the 2500 units/cc. concentration and up flocculation was produced which obscured the gross reading by turbidity, so that growth was confirmed by plating on EMB agar. After 48 hours of treatment with oral streptomycin the high streptomycin concentration tubes were found to contain heavy growth. The zone of inhibition, between 156 units/cc. and 2500 units/cc., was also confirmed since plating on EMB agar produced no growth or scant growth.

These observations indicate that resistant strains of *E. Coli* develop with great rapidity within 48 hours after institution of streptomycin.

The fact that *E. Coli* may be inhibited by concentrations of streptomycin below 2500 units/cc. and yet not be killed by concentrations between 2500 units/cc. and 10,000 units/cc. is a phenomenon of considerable interest, and calls attention to a related phenomenon described by Eagle,¹¹ who observed a similar zone effect with penicillin.

STOOL ASSAY FOR STREPTOMYCIN CONTENT

The stools of three patients who were given 4 Gm. of streptomycin daily divided 1 Gm. every six hours were assayed for streptomycin content. It was found that within 48 hours after the initiation of therapy a level of 4,800 to 9,600 units of streptomycin per gram of wet stool was reached. One patient was found to have 19,200 units/gram after six days of oral streptomycin. It will be noted that these concentrations are greater than the prozone levels observed in the titrations, and are in the range where streptomycin resistant organisms proliferate.

ORAL STREPTOMYCIN COMBINED WITH SULFATHALADINE

Because of the unreliable results obtained with oral streptomycin alone, a series of preoperative patients were given oral streptomycin in combination with sulfathaladine, and daily colony counts of the stools by the method previously described were carried out. Dosages given were 0.25 Gm. of streptomycin and 1 Gm. sulfathaladine every six hours by mouth. Though this series is too small to permit valid conclusions the data on the nine cases so treated are here reported, since they appear to show results essentially similar to the response obtained with oral streptomycin alone (See Table III). It will be noted that only four of the nine cases showed a significant drop in the numbers of coliform and streptococcus colonies.

In all four of these cases the effect was short-lived, the maximum reduction in the bacterial flora occurring within 48 to 72 hours after the institution

of treatment, and thereafter returning very rapidly to the pretreatment level, this level becoming re-established within five days after the institution of chemotherapy and within two days after the maximum drop. Only one of the nine cases showed a significant drop in the number of clostridia colonies, and this was temporary. All nine patients were followed at least four days, the longest being nine days. No toxic effects were observed in this series of cases.

TABLE III.—*Response of Colony Counts to 1.0 Gm. Streptomycin and 4.0 Gm. Sulfathaladine Per Day*

Degree of Response	Number Giving No Response	Number Giving Temporary Response		Number Giving Prolonged Response		Total Number of Cases
		To 0.01%	To 0.001% or Less	To 0.01%	To 0.001% or Less	
<i>E. Coli</i>	5	1	3	0	0	9
Streptococci	5	4	0	0	0	6
<i>Cl. welchii</i>	8	1	0	0	0	6

CONCLUSIONS

A comparison of the results reported in this paper with previous publications has led us to the conclusion that oral streptomycin cannot be recommended for the preoperative preparation of patients requiring large bowel surgery, for the following reasons:

- (1) Reduction in intestinal flora is unpredictable and unreliable.
- (2) In a significant proportion of the cases which show a favorable early response to oral streptomycin, the organisms rapidly develop resistance to the drug.

Although our series of cases is too small to permit final conclusions to be drawn it would seem that the probable development of resistance to streptomycin by the intestinal organisms would be likely to render the parenteral use of this drug ineffective should the patient develop postoperative complications which might ordinarily be treated with this drug. In view of these observations we feel that it would be wiser to reserve the use of streptomycin for the treatment of complications should they develop rather than to expend the drug effect in the preoperative preparation of the patient.

SUMMARY

1. A review of publications on the use of oral streptomycin in preoperative preparation of surgical cases is presented. The conflicting nature of those reports is emphasized.
2. A series of 24 cases treated at the Presbyterian Hospital with oral streptomycin is presented, together with the methods used to obtain serial quantita-

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tion colony counts on the three groups of organisms studied, the coliform group, the streptococcus, and the clostridia.

3. Results obtained were inconsistent. Approximately half of the cases treated showed no response in the coliform group to oral streptomycin, and of the cases showing a response, 50 per cent or $\frac{1}{4}$ of the total number of cases, showed a prolonged significant response.

4. Eighty-seven and seven-tenths per cent of the cases showed no significant reduction in the number of streptococci present in the stool.

5. Thirty-eight and nine-tenths per cent of the cases showed no significant reduction in the number of clostridia present in the stool.

6. Sensitivity titrations on the *E. Coli* group showed rapid development of resistance to streptomycin, and brought out the fact that many strains of *E. Coli* become able to proliferate in the concentrations of streptomycin which exist in feces.

7. A series of nine cases treated with combined streptomycin and sulfathaladine is presented. The results in this group are also inconsistent.

8. The authors conclude that oral streptomycin is unpredictable and unreliable, and its use in the preoperative preparation of surgical cases is not to be recommended.

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THE IMPORTANCE OF THE LEVEL OF THE LESION IN THE PROGNOSIS AND TREATMENT OF CARCINOMA OF THE RECTUM AND LOW SIGMOID COLON*

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IT IS NO LONGER POSSIBLE to be complacent about the adequacy of combined abdominoperineal resection, done in the classic fashion, in the treatment of carcinoma of the rectum and lower part of the sigmoid colon. This procedure, the result of the careful studies and the experience of Miles, unquestionably represents a logical and important advance in surgical management of malignant disease. However, it, in common with all operations, is constantly challenged by changing concepts, new information and advances in surgical technic.

It has been the practice of many surgeons to employ the operation of combined abdominoperineal resection in the treatment of all lesions of the rectum, and in those lesions of the sigmoid colon located so low that an exteriorization operation of some type is not possible. This concept of treatment has been questioned in recent years on two general scores. On the one hand, in cases in which there are lesions of the upper part of the rectum, the rectosigmoid and the lower part of the sigmoid colon, it has been proposed^{1, 8, 20, 22-24} that operations as curative as combined abdominoperineal resection can be done which will at the same time conserve sphincteric function to some degree at least; secondly, it has been questioned whether the usual Miles operation is as curative for low-lying rectal and anal lesions as a more radical posterior excision.⁹

That the life and comfort of patients suffering from carcinoma of the terminal portions of the colon depend on an accurate answer to these questions is obvious. There can be no challenge to the contention that in carcinoma of the rectum and sigmoid colon, the operation which is proved to be the most efficacious in effecting cure should be done, regardless of whether or not a permanent abdominal colonic stoma is necessary. This assumes of course that differences in operative mortality rates in good risk patients are negligible, which we believe to be true. However, it would seem equally obvious that two procedures which are equally curative but in one of which preservation of the function of the anal sphincter is possible and in the other of which a permanent abdominal colonic stoma must be made are not of equal merit. An

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accurate appraisal of this situation demands an unbiased analysis of the factors involved.

The determination of truly comparable survival rates in patients undergoing combined abdominoperineal resection, and in those undergoing the other procedures which have arisen to challenge it, is not as simple as might appear. It is well known that operability rates, resection rates and hospital mortality rates must be known for each procedure to be considered and must be carefully controlled. More important, and perhaps less well appreciated, is that there are many factors inherent in the growth itself which should be analyzed and understood with relation to such comparisons of the various operative procedures.

These factors, in addition to being important in the use of comparative statistical data, are important in considering the adoption of a relatively new and as yet unproved operative procedure. Obviously, it is not as yet possible to compare accurately the results from combined abdominoperineal resection, posterior resection, the Hochenegg pull-through procedure, perineal resection with primary anastomosis, anterior resection with primary anastomosis and the other procedures which have been employed for lesions in this region. Until such comparisons are possible, the surgeon should understand as thoroughly as possible the behavior of the growths in question and the factors affecting their prognosis. In this way, he may select a procedure which, though as yet unproved, is based on sound reasoning.

The histologic grade (Broders) of the lesion and the extent of the lesion as represented by its type (Dukes)¹¹ are two outstanding factors which must be studied and understood in any series of rectal and low sigmoidal carcinomas. It would seem that the location of the lesion, with respect to its distance from the anal margin, might also be a factor of some importance. Obviously, in comparing the survival rates of patients treated by anterior resection with those of patients treated by combined abdominoperineal resection, one should know, among other things, whether there is any difference in the prognosis of low-lying rectal lesions and of low sigmoidal lesions, when both are treated by combined abdominoperineal resection. If the low sigmoidal lesions have a significantly better prognosis than the low-lying rectal lesions, when both are treated by the same operative procedure, then one must of course compare the survival rates after anterior resection, with restoration of intestinal continuity, *not* with those of all patients treated by abdominoperineal resection, but with those of patients having lesions at the same level of the bowel as the patients treated by anterior resection. Furthermore, if it were shown that patients having low-lying rectal lesions treated by combined abdominoperineal resection fare less well than those having lesions in the middle and upper parts of the rectum, it might be an impetus to the trial of a more radical removal of the very low-lying lesions.

It was because of these implications that a study was made of the effect of the level of the lesion on the prognosis in carcinoma of the rectum and the lower part of the sigmoid colon.

REVIEW OF THE LITERATURE

A careful review of the literature has failed to reveal a factual analysis allowing accurate conclusions as to the effect of the level of the lesion in the bowel on prognosis after surgical resection of the growth in cases of carcinoma of the rectum or sigmoid colon. There have been opinions expressed concerning this matter, however, some of which have of course been conflicting.

Lockhart-Mummery, in 1926, stated that patients having adenocarcinomas of the rectosigmoidal junction had a poorer prognosis than those having lesions in the rectum itself; he felt that one reason for this was the greater difficulty associated with removal of the regions of direct spread and nodal involvement in rectosigmoidal lesions. Coffey, in 1931, again expressed the opinion that patients having rectosigmoidal lesions are more difficult to cure than those having the lower-lying rectal lesions.

Dukes has carefully and accurately studied many phases of the pathology of rectal and sigmoidal cancers, but there are not available in his published work data as to the effect of the level of the lesion itself on the curability of the lesion. He stated¹² that he had concluded that in cases without involvement of lymph nodes the five year survival rates are the same regardless of location. However, he stated that in lesions with nodal involvement the results "varied to some extent with the position in the rectum of the malignant growth." It was his opinion that lesions in the midrectal region did less well than those in a similar stage of development located in the upper or lower part of the rectum. He felt that this was due to the more pronounced tendency for lateral spread in lesions in the midrectum.

Gilchrist and David,^{14, 15} in two recent publications, set forth some results of their careful studies of carcinoma of the bowel, which indicate that in their cases the low-lying lesions entailed a poorer prognosis than the higher-lying ones. They called the low-lying group the "extraperitoneal group." Since it has been shown in a previous study¹⁸ that the location of the growth with reference to the level of the peritoneal reflection has no effect on prognosis, other factors being equal, it may well be that the poorer prognosis in the "extraperitoneal group" of Gilchrist and David is due to their low location in the rectum, rather than to their being beneath the peritoneal reflection.

Barbosa, Waugh and Dockerty studied 105 cases of low rectal and anal adenocarcinomas and concluded from their study that the prognosis in these cases is poorer than in higher-lying rectal lesions.

Thus there is considerable suggestion in the recent literature that there is some relation between the level of the lesion and the prognosis. What data are available tend to support the idea that the lower-lying lesions have, in general, a poorer prognosis than the higher-lying ones.

MATERIALS AND METHODS OF STUDY

From the files of the Mayo Clinic were selected the records of all patients

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who, in the ten year period from 1931 through 1940, had undergone combined abdominoperineal resection for adenocarcinoma of the rectum and sigmoid colon and who had survived operation. All cases with metastatic growths in the liver or other distant sites, and thus in which the resection was purely palliative, were eliminated. The records of 453 patients were thus obtained. On careful review of the record of each patient, it was found that 65 cases were not suitable for inclusion in this study. A few had been incorrectly filed, and were in fact palliative resections; a few had had only the first stage of a two-stage combined abdominoperineal resection and for some reason had failed to have the second stage. Most of these 65 were not suitable for inclusion in this study because no accurate data were available as to the level of the lesion within the bowel. It should be stated that nearly all these cases with data insufficient to judge accurately the level of the lesion occurred in the first few years of the study, at a time when proctoscopic estimation of the level of the lesion was not routinely performed.

Three hundred and eighty-eight cases remained for study. Data were available in each case, from proctoscopic examination, digital examination of the rectum, from the surgeon's note and from the pathologic examination, as to the approximate level of the lesion. In general, the data from these various sources agreed. However, the data from proctologic examination were usually most clearly stated, since it has been the policy in the clinic for some time to report lesions as beginning a given number of centimeters above the anal margin. Because of this, and because clinically this proctoscopic estimation of the level of the lesion is of value in the planning of the surgical procedure, the distance from the anal margin as estimated by the proctoscopist has been used in classifying these lesions.

It is to be noted that the lesions thus are classified according to the distance from the anal margin to the lower edge of the lesion. It is freely acknowledged that this is not a really precise method of locating the lesions, but it has two advantages over a seemingly more precise method; namely, the measurement of this distance in formalin-preserved surgical specimens. In the first place, as noted previously, it is the most important preoperative method of estimating the level of the lesion. Secondly, there is considerable shrinkage in preserved specimens, and thus an accurate idea of the level of the lesion *in vivo* may not be obtained from a study of them.

Note was made in each case of the histologic grade of the lesion and of the presence or absence of nodal involvement, as reported by the pathologist examining the surgical specimen. The follow up correspondence was carefully reviewed to determine the survival or death of each patient in the series. Analysis by the direct method was then made of the five-year survival rates of patients having lesions at various levels in the bowel.

RESULTS

The results of this study are presented in a series of tables, which are in the main self-explanatory. These data allow the formation of certain con-

clusions as regards the effect of the level of the lesion on survival rates after combined abdominoperineal resection.

It appears (Table I) that those patients whose lesions lie within approximately 5 cm. of the anal margin have a poorer prognosis than those whose lesions lie above this level, both groups being treated by combined abdominoperineal resection. Those patients having lesions approximately 11 cm. or more above the anal margin have a prognosis which is slightly better than that of the over-all group but in cases with nodal involvement these persons with high-lying lesions would seem to have a definitely better prognosis than those with either low-lying lesions or with lesions the lower edge of which ranges from 6 to 10 cm. from the anal margin.

TABLE I.—*Survival Rates of Patients Having Adenocarcinoma of the Rectum and Sigmoid Colon Treated by Combined Abdominoperineal Resection*

Level of Lower Edge of Lesion Above Anal Margin	Nodal Metastasis	Patients	Traced Patients	Lived 5 or More Years After Operation	
				Number	Per Cent of Traced Patients*
0-5 cm.	All cases	100	93	43	46.2
	Without	56	50	33	66.0
	With	44	43	10	23.3
6-10 cm.	All cases	201	182	93	51.1
	Without	105	94	71	75.5
	With	96	88	22	25.0
11 cm. or more	All cases	87	80	43	53.8
	Without	54	47	32	68.1
	With	33	33	11	33.3

* In this and all subsequent tables, inquiry was as of January 1, 1946. All operations were performed in 1940 or earlier.

In order to obtain a more homogeneous group for analysis, the 248 cases in this series in which the lesions showed grade 2 (Broders) malignancy were analyzed in similar fashion (Table II). These data show the same general trend as those of the entire group, but the differences are more clear-cut. We believe that this group represents more accurately the true state of affairs, since the lesions are histologically similar through the group. It is again seen that patients whose lesions were within 5 cm. of the anal margin had a poorer prognosis than those with lesions lying higher up and that those with lesions lying 6 to 10 cm. removed from the anal margin had a poorer prognosis than those with lesions 11 cm. or more removed from this point. Again, considering only lesions with nodal involvement, a location 11 cm. or more removed from the anal margin allowed a much more favorable prognosis than did a lower location. In the group with grade 2 lesions without nodal involvement, those patients with low-lying lesions again appear to have

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a prognosis less favorable than those with growths lying 6 cm. or more above the anal margin.

In order to obtain some further information on the critical levels, as regards prognosis, the data were again analyzed, this time breaking the cases down into groups at somewhat different levels (Table III).

TABLE II.—*Survival Rates of Patients Having Grade 2 Adenocarcinoma of the Rectum and Sigmoid Colon Treated by Combined Abdominoperineal Resection*

Level of Lower Edge of Lesion Above Anal Margin	Nodal Metastasis	Patients	Traced Patients	Lived 5 or More Years After Operation	
				Number	Per Cent of Traced Patients
0-5 cm.	All cases	72	66	30	45.5
	Without	41	36	22	61.1
	With	31	30	8	26.7
6-10 cm.	All cases	119	106	56	52.8
	Without	62	55	41	74.5
	With	57	51	15	29.4
11 cm. or more	All cases	57	51	31	60.8
	Without	34	28	21	75.0
	With	23	23	10	43.5

TABLE III.—*Survival Rates of Patients Having Adenocarcinoma of the Rectum and Sigmoid Colon Treated by Combined Abdominoperineal Resection*

Level of Lower Edge of Lesion Above Anal Margin	Nodal Metastasis	Patients	Traced Patients	Lived 5 or More Years After Operation	
				Number	Per Cent of Traced Patients
0-2 cm	All cases	61	58	25	43.1
	Without	34	31	18	58.1
	With	27	27	7	25.9
3-6 cm.	All cases	77	70	33	47.1
	Without	41	36	27	75.0
	With	36	34	6	17.6
7-10 cm.	All cases	163	148	77	52.0
	Without	86	77	58	75.3
	With	77	71	19	26.8
11 cm. or more	All cases	87	80	43	53.8
	Without	54	47	32	68.1
	With	33	33	11	33.3

This tabulation again serves to emphasize the relatively poor prognosis in patients with very low-lying rectal carcinomas. Thus, persons with lesions lying within 2 cm. of the anal margin have, in the over-all group, a prognosis

which is less favorable than those with growths at any other level. In those with growths above this point, the prognosis gradually improves as the higher levels of the rectum are reached. It is interesting to note, in addition, that in cases with nodal involvement, the group with lesions lying 3 to 6 cm. up from the anal margin had the poorest prognosis while those with lesions within 2 cm. of the anal margin were only slightly better. The prognosis of lesions above 11 cm. again was superior to that at any other level. Except for patients with lesions within 2 cm. of the anal margin, in which instance the prognosis was poor, in lesions without nodal involvement there was not any significant improvement in prognosis as the higher levels were reached.

The data were similarly analyzed for grade 2 lesions only (Table IV). This more homogeneous group serves to substantiate the tendencies indicated by the over-all group thus analyzed.

TABLE IV.—*Survival Rates of Patients Having Grade 2 Adenocarcinoma of the Rectum and Sigmoid Colon Treated by Combined Abdominoperineal Resection*

Level of Lower Edge of Lesion Above Anal Margin	Nodal Metastasis	Patients	Traced Patients	Lived 5 or More Years After Operation	
				Number	Per Cent of Traced Patients
0-2 cm.	All cases	44	41	17	41.5
	Without	26	23	12	52.2
	With	18	18	5	27.8
3-6 cm.	All cases	51	45	23	51.1
	Without	28	24	18	75.0
	With	23	21	5	23.8
7-10 cm.	All cases	96	87	46	52.9
	Without	49	45	33	73.3
	With	47	42	13	31.0
11 cm. or more	All cases	57	51	31	60.8
	Without	34	28	21	75.0
	With	23	23	10	43.5

COMMENT

It is apparent that patients with lesions lying very near the anal margin, treated by combined abdominoperineal resection, have a prognosis which is poorer than those with higher-lying lesions removed by the same operation. This unfavorable group probably embraces those patients having a lesion, the lower margin of which is within 5 or 6 cm. of the anal margin, as estimated by proctoscopy. Patients with lesions, the lower margins of which are 6 or 7 to 10 cm. removed from the anal margin, have a somewhat better prognosis, whether the growth is with or without nodal involvement, than patients with low-lying lesions; while those with lesions 11 cm. or more from the anal margin have a prognosis superior to that of patients with lesions

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lying below this level. These differences are not in every instance of great magnitude, but they do seem to indicate a consistent and definite difference in the behavior of lesions at varying levels in the bowel.

That such a difference occurs necessitates a consideration of two points. One of these is the possible basis for this difference in prognosis. The second is the application of a knowledge of these differences to the selection of operative procedures for carcinoma of the rectum and sigmoid, and to the interpretation of the results of these operations.

It is unlikely that there is any inherent variation in the malignancy of adenocarcinomas at varying levels of the bowel. Certainly there has not been demonstrated any tendency to higher grade lesions in growths located low in the rectum. Further, the differences in prognosis in this study were as significant, if not more so, when only grade 2 (Broders) lesions were considered as when the over-all group was analyzed. It has been suggested by some^{4, 24} that there is a slightly higher incidence of venous involvement and thus of visceral metastatic growths in the high-lying rectal lesions and low sigmoidal lesions than in the lower rectal lesions, although Dukes¹² stated that he found such involvement with equal frequency in all regions of the rectum and lower part of the sigmoid. If this slight difference does in fact exist, then the poorer prognosis of patients with low lesions occurs in spite of it, rather than because of it. It is doubtful indeed that differences in extent of invasion, as reflected in the typing of lesions after the method of Dukes, are responsible for differences in prognosis here, since these differences in prognosis are present when only cases with demonstrable nodal involvement are considered. It is further unlikely that the unfavorable tendencies of the low-lying lesions are due to their location beneath the peritoneal reflection, since it has been shown¹⁸ that the relation of growths to this reflection *per se* does not have any effect on prognosis.

The failure of combined abdominoperineal resection to effect as high a survival rate in patients with low-lying lesions may well, on the other hand, be due to its failure to cope with certain routes of lymphatic spread of the low-lying lesions. Without going into needless detail, it may be mentioned that there are, at least in theory and probably in fact, three routes of lymphatic spread in the lesions under consideration. These are of course, first, upward alongside the superior hemorrhoidal and inferior mesenteric vessels; second, laterally, along the lymphatic pathways accompanying the middle hemorrhoidal vessels and lying along the levator ani muscles; and third, inferiorly, along lymphatics destined eventually to accompany the inferior hemorrhoidal vessels and to drain in occasional instances to the superficial inguinal lymph nodes.

The differences in prognosis encountered in this study cannot be explained on the basis of differences in the efficacy of the operation in eradication of the upward spread in these lesions, for then one might expect the prognosis of the high lesions to be poorer than that of the low ones. Failure to excise adequately the inferior lymphatic spread of these lesions is not a probable explanation for several reasons. It has been demonstrated amply

by several careful studies^{6, 13, 16, 17} that spread along this inferior route is very uncommon in lesions of the upper part of the rectum and of the recto-sigmoid, and it has been recently emphasized by the careful studies of Dafoe that retrograde, or downward, lymphatic spread is likewise very unusual in the low-lying lesions of the rectum.

However, it is possible that the differences in curability of the low-lying lesions, in contrast to those more removed from the anal margin, are due to spread along the lateral route, as has been suggested by others.

Miles expressed the belief that lateral spread was the least important of the three possible lymphatic pathways. However, studies on lateral lymphatic spread in carcinoma of the rectum are by no means numerous or conclusive. One reason for this is that even with combined abdominoperineal resection, only a relatively small amount of tissue lateral to the growth is removed, and thus only a small amount is available for study of spread in this direction. Most of the tissue of real interest in this mode of spread remains within the patient after operation. Dukes¹² as previously noted, expressed the opinion that lesions in the midrectal region did less well than similar growths in the lower or in the upper part of the rectum because of the tendency of the ampullary lesions to grow laterally along the lymphatics accompanying the middle hemorrhoidal vessels. Gilchrist and David¹³ noted, in their study of this problem, that 4 of 47 surgical specimens studied showed lateral nodal involvement along the superior surface of the levator ani muscle; these cases appeared to have lesions the lower margins of which were approximately 5 cm. or more from the anal margin. In addition, in one of the two necropsy cases that they reported, in both of which the patients died a few days after combined abdominoperineal resection, there was a single involved node left behind, situated about 1 cm. lateral to the point of severance of the levator ani muscle.

Coller, Kay and MacIntyre, who likewise made an extensive and thorough study of metastatic growths in lymph nodes in cases of carcinoma of the rectum, also noted good evidence of lateral lymphatic spread occurring in cases in which the superior route of spread was *not* blocked. Thus, in one of their necropsy cases, with a grade 2 carcinoma right at the anal margin, there were only seven nodes involved, all these being along the course of the right middle hemorrhoidal artery. Also, they pointed out that in seven of their 19 cases of very low-lying rectal cancers there was evidence of nodal involvement up to the margin of the excision of the levator ani muscle, which certainly must be construed as evidence of lateral spread. Further, these were not cases showing choking of the upper lymphatics. They further noted that in no lesion in which the inferior border was 3 cm. or more above the mucocutaneous junction (which would probably correspond to a level about 5 cm. above the anal margin as estimated by proctoscopy) did they find metastatic growths along the lateral zone of spread.

Dafoe also has studied the lateral spread of carcinomas lying within 4.5 cm. of the pectinate line, in a careful dissection of 100 specimens of such far-

advanced cases. He again noted evidence in the removed specimens of lateral spread, but the presence of such spread in these far-advanced cases has somewhat less significance than in the less extensive cases studied by some other investigators.

In summary, it is nearly certain that lateral spread does occur occasionally in those far-advanced cases in which there is blockage of the superior zone of spread. It is further very probable, from the data recorded in the literature, that it also occurs fairly often in less extensive lesions the lower margins of which are within 5 or 6 cm. of the anal margin, as estimated by proctoscopic examination; and that in point of fact in such instances, it, along with the superior zone of spread, is a normal route of lymphatic metastasis and not an abnormal one taken only when the so-called normal routes are plugged with malignant deposits.

Such lateral spread beyond the line of resection carried out by the combined abdominoperineal operation is the probable explanation for the inferior prognosis in patients with lesions lying within 6 cm. of the anal margin. In lesions the lower margins of which were above this level, the lateral zone of spread was probably rarely involved, and thus failure to excise it completely in the resection did not lessen the chances for survival of the patient. It is not immediately apparent why patients with lesions the lower margins of which lay 3 to 6 cm. above the anal margin seemed to have a somewhat poorer prognosis than those with lesions in contiguity to the anus, when nodes are involved.

These matters have a very practical importance to the surgeon called on to treat malignant lesions of the rectum and sigmoid colon, for they influence to a great extent his choice of the surgical procedure for a given patient. As stated in the opening of this paper, this has become so since the classic combined abdominoperineal resection is now challenged in the treatment both of low-lying rectal lesions and of rectosigmoidal and sigmoidal lesions.

It is to be noted that the mere occurrence of a less favorable prognosis in patients with low-lying rectal lesions does not mean that it is possible to improve the prognosis in this group by more extensive surgical treatment.

Yet, it does become justifiable to inquire if a more radical removal of tissue in the region of lateral spread is possible in lesions within 5 or 6 cm. of the anal margin. Dixon⁹ has suggested that radical posterior resection, preceded by the formation of an abdominal colonic stoma and ligation of the superior hemorrhoidal vessels at a first stage, may in fact entail a more thorough removal of tissue in this region. A study of survival rates in a group of cases in which lesions the lower margins of which are within 5 or 6 cm. of the anal margin are treated by such a resection may help answer this problem, when compared to the survival rates in a similar group treated by the Miles operation.

Further, it has in recent years seemed proper to a number of surgeons to discard abdominoperineal resection for early or moderately advanced lesions the lower margins of which are 11 cm. or more removed from the anal margin, in favor of anterior resection with primary anastomosis.^{8, 16, 25} It is our opinion that this is justifiable, and indeed desirable, on the basis of the data previously

referred to concerning lymphatic spread of such lesions. The survival rates at present available confirm this conclusion.¹⁰

There remains a borderline zone, extending from 5 or 6 cm. above the anal margin to 10 or 11 cm. above this point. It is very difficult to effect an anastomosis safely after resection of a growth located in this region; yet the rarity of lateral and retrograde spread in such lesions strongly suggests that sacrifice of the perineum and anal sphincters is not necessary. Thus a combined abdominoperineal resection with preservation of the anal sphincters^{1, 23} has seemed to us to be the advisable procedure for growths located in this region. It should be emphasized, however, that the final decision as to whether this procedure, segmental resection with restoration of intestinal continuity, or the Miles operation is to be performed in a given case can be made only at the operative table after mobilization of the sigmoid, rectosigmoid and upper part of the rectum.

A final judgment as to the efficacy of this sphincter-conserving operation as well as to that of other operations employed for lesions in this region must depend on a carefully controlled comparison between the survival rates allowed by them and those procured by the classic combined abdominoperineal resection for lesions at comparable levels in the bowel.

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MALIGNANT TUMORS OF THE COLON AND RECTUM*

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MALIGNANT TUMORS OF THE COLON and rectum were found at Duke Hospital in 441 patients during the 15-year period 1931-1945. The incidence, symptomatology, treatment and results in this group have been analyzed and form the basis of this report.

INCIDENCE

Tabulation by site, sex, and color is shown in Table I, and by age in Table II. The frequency of these lesions as compared with the number of hospital admissions gradually increased until the last five years when the rate practically stabilized at one patient in every 337 admissions having a malignant tumor of the colon or rectum.

HISTORY

Twenty and four-tenths per cent of this group gave a family history of malignant tumor. The accuracy as to site was frequently questionable, but lesions most commonly occurred in the stomach, uterus and cervix, bowel, and skin in that order.

Operations performed before coming to Duke Hospital but after the onset of symptoms which ultimately led to the diagnosis of malignancy were: Colostomy 11, ileostomy two, resection of tumor five, exploratory laparotomy nine, appendectomy four, and biopsy of rectal lesion four. The infrequency of rectal biopsy is emphasized. Hemorrhoidectomy or repeated injections for hemorrhoids were carried out in 9 per cent of patients with lesions of the rectum or rectosigmoid. Most surgery for lesions proximal to the rectosigmoid had been emergency procedures, usually for intestinal obstruction.

The duration of symptoms, calculated from onset of first symptom to time of reporting to the hospital, averaged 8.7 months for the entire group, and varied from 6.3 months in the hepatic flexure group to 11.7 months for lesions of the splenic flexure. In three patients small lesions were found during operation for causes other than carcinoma and thus were diagnosed prior to the onset of symptoms. Much difficulty was encountered in determining the time of change from a benign lesion to malignancy in patients with polyposis. Table III shows the duration of symptoms in each group by economic status, *i.e.*, service or private.

In the detailed consideration of symptoms, signs and accessory clinical data, the consolidation of the lesions into three groups instead of nine appeared justified because of the similarity of these findings. The cecum, ascending

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colon and hepatic flexure were grouped as the right colon; the transverse colon, splenic flexure, descending colon, and sigmoid as the left colon; and the rectosigmoid and rectum considered as the third group.

The symptoms in each group are shown in Tables IV, V, and VI; and in Table VII, the most frequent symptoms are compared. In two of the left colon

TABLE I.*—Site, Sex and Race of 441 Malignant Tumors of Colon and Rectum.

Site	Total		Male		Female		White		Colored	
	No.	%	No.	%	No.	%	No.	%	No.	%
R	229	51.9	127	55	102	45	179	78	50	22
RS	29	6.6	18	62	11	38	27	93	2	7
S	63	14.3	35	55	28	45	53	84	10	16
DC	20	4.5	6	30	14	70	19	95	1	5
SF	8	1.8	7	87	1	13	6	75	2	25
TC	8	1.8	3	37	5	63	6	75	2	25
HF	17	3.9	10	59	7	41	15	88	2	12
AC	23	5.2	15	65	8	35	21	91	2	9
C	44	10.0	30	68	14	32	40	91	4	9
Total	441		251	57	190	43	366	83	75	17

*(In this and subsequent tables, all abbreviations for site of lesions are: R, rectum; RS, rectosigmoid; S, sigmoid; DC, descending colon; AC, ascending colon; SF, splenic flexure; TC, transverse colon; HF, hepatic flexure; C, cecum.)

TABLE II.—Distribution by Age.

	10-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
R	1	9	24	36	60	77	18	4
RS	0	2	3	6	8	7	3	0
S	0	3	4	12	20	18	6	0
DC	1	1	0	1	3	2	0	0
SF	0	1	2	3	5	6	2	1
TC	0	0	1	1	1	4	1	0
HF	0	2	2	7	2	2	2	0
AC	1	0	2	2	9	7	2	0
C	1	3	3	8	13	11	5	0
Total No.	4	21	41	76	121	134	39	5
Total %	0.9	4.8	9.3	17.2	27.4	30.4	8.9	1.1

group and 13 of the rectum and rectosigmoid group, the first symptom was not clearly enough differentiated to permit inclusion. In 7 per cent of patients with lesions of the right colon and only 5 per cent of those of the left colon, intestinal obstruction came on rapidly in the absence of earlier symptoms. As would be expected, however, intestinal obstruction (as indicated by constipation, nausea, vomiting and distention) was more frequent with left colon lesions. Of the 84 patients with right colon lesions in this series, 23 per cent felt an abdominal mass, 29 per cent had marked weakness, and the remainder various gastro-intestinal complaints. Four (5 per cent) patients felt a mass and 12 (14 per cent) noted weakness, prior to the onset of other symptoms.

Changes in bowel habit and stool were frequent in all patients, but such symptoms predominated in the rectum and rectosigmoid group. Blood and mucus in the stool, constipation, diarrhea, and more localized symptoms such as tenesmus, decreased caliber of stool and rectal fullness occurred repeatedly. Symptoms of obstruction were not as common as in the left colon group. A not infrequent history was that of melena lasting only a day or two followed by an asymptomatic period of several months before characteristic symptoms appeared.

TABLE III.—*Duration of Symptoms in Months Prior to Reporting to Hospital.*

	R	RS	S	DC	SF	TC	HF	AC	C
Average	8.8	9.4	8.6	6.9	11.7	8.0	6.3	10.1	8.5
Service	9.6	10.3	9.6	6.1	10.4	4.0	6.3	10.8	7.1
Private	7.3	8.4	7.3	7.4	15.0	8.6	6.3	8.6	9.3

TABLE IV.—*Symptoms in 84 Patients with Lesions of the Right Colon. Number in parentheses indicates frequency as first symptom.*

Abdominal pain.....	62 (48)	Vomiting.....	17 (0)
Weakness.....	24 (12)	Constipation.....	15 (1)
Melena.....	23 (4)	Diarrhea.....	12 (6)
Nausea.....	20 (0)	Anorexia.....	11 (0)
Abdominal mass.....	19 (4)	Distention.....	7 (1)
		Alternating diarrhea and constipation.....	2 (0)
		Acute obstruction as first symptom.....	5

TABLE V.—*Symptoms in 99 Patients with Lesions of the Left Colon. Number in parentheses indicates frequency as first symptom.*

Abdominal pain.....	71 (33)	Alternating diarrhea and constipation.....	10 (4)
Melena.....	53 (10)	Abdominal mass.....	10 (3)
Constipation.....	42 (22)	Mucus in stool.....	10 (0)
Nausea.....	25 (0)	Tenesmus.....	8 (0)
Vomiting.....	23 (0)	Anorexia.....	4 (0)
Distention.....	22 (3)	Urinary.....	3 (0)
Diarrhea.....	20 (12)	Rectal fullness.....	2 (0)
Weakness.....	13 (3)	Aching rectal pain.....	1 (1)
Decreased caliber of stool....	12 (1)		
		Acute obstruction as first symptom.....	5

Although abdominal pain was the most frequent symptom in both colon groups, and fifth most common in the rectum and rectosigmoid group, no detailed analysis as to location, severity, character or radiation of the pain was made. Variation in these manifestations was dependent upon site of lesion, degree of obstruction, involvement of other organs, presence of infection, and probably other factors.

In 239 of the 441 records, the amount of weight loss was stated. The average for this group was 25.6 pounds. The average loss for 138 of the 258 patients with lesions of the rectum and rectosigmoid was 24.2 pounds, for 57 of the 99 left colon lesions 24.6 pounds, and for 45 of the 84 right colon lesions 31.5 pounds (Table VIII).

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EXAMINATION

The findings of principal interest on physical examination pertained to the abdomen, and Table IX summarizes the most frequent signs. Tenderness was usually found over the site of the lesion and was infrequently severe. The signs of peritoneal irritation occurred with complications such as obstruction or perforation. Distention was a fairly common finding and varied in severity depending on the degree of obstruction. There were 33 patients classified as

TABLE VI.—*Symptoms in 258 Patients with Lesions of the Rectum and Rectosigmoid. Number in parentheses indicates frequency as first symptom.*

Melena.....	220 (80)	Aching rectal pain.....	20 (14)
Constipation.....	115 (62)	Inability to empty.....	15 (0)
Tenesmus.....	77 (10)	Urinary.....	14 (0)
Diarrhea.....	73 (40)	Distention.....	13 (0)
Abdominal pain.....	68 (18)	Alternating diarrhea and constipation.....	12 (4)
Mucus in stool.....	60 (3)	Anorexia.....	7 (0)
Decreased caliber stool.....	58 (3)	Nausea.....	7 (0)
Weakness.....	23 (6)	Vomiting.....	7 (0)
Rectal fullness.....	23 (5)	Abdominal mass.....	3 (0)

TABLE VII.—*A Comparison of the Five Most Frequent Symptoms in Each Group.*

Rectum and Rectosigmoid (258 Patients)	Left Colon (99 Patients)	Right Colon (84 Patients)
Melena.....	220 (85%)	Abdominal pain 71 (72%)
Constipation.....	115 (46%)	Melena..... 53 (53%)
Tenesmus.....	77 (30%)	Weakness..... 24 (29%)
Diarrhea.....	73 (28%)	Constipation... 42 (42%)
Abdominal pain	68 (26%)	Melena..... 23 (27%)
		Nausea..... 20 (24%)
		Vomiting..... 19 (23%)

TABLE VIII.—*Weight Loss in Pounds.*

	5-20	21-40	41-60	61-80	81-100
Rectum and rectosigmoid	72 (52.2%)	50 (36.4%)	9 (6.5%)	5 (3.6%)	2 (1.5%)
Left colon.....	32 (56.1%)	17 (29.9%)	4 (7.0%)	4 (7.0%)	0
Right colon.....	15 (33.4%)	19 (42.3%)	7 (15.5%)	2 (4.4%)	2 (4.4%)

completely obstructed who required immediate surgical intervention or, in a few instances, prolonged nonoperative treatment to relieve the obstruction. An abdominal mass was more often palpable in lesions of the right colon than elsewhere.

Of 229 cases of rectal malignancy, the lesion was felt by digital examination in 222, not felt but seen by proctoscopy in five, and no examination was recorded in two. Details regarding the lesion were recorded with variable accuracy. The mass was described as movable in 36 and fixed in 54. In position, it was on the right in eight, left in 13, anterior in 26, posterior in 23, and encircled the rectum in 64.

Complicating and intercurrent diseases were found as follows: Hypertensive vascular disease 82, cardiac disease with decreased reserve 24, obesity 20,

diabetes three, pulmonary tuberculosis one, bronchiectasis one, hyperthyroidism one, chronic alcoholism one, and senile dementia one. Generalized arteriosclerosis, benign prostatic hypertrophy, secondary anemia, and similar diagnoses were not tabulated.

The extent of the laboratory examinations depended on the indications, but all patients had at least hemoglobin, white blood cell count, blood serology, and

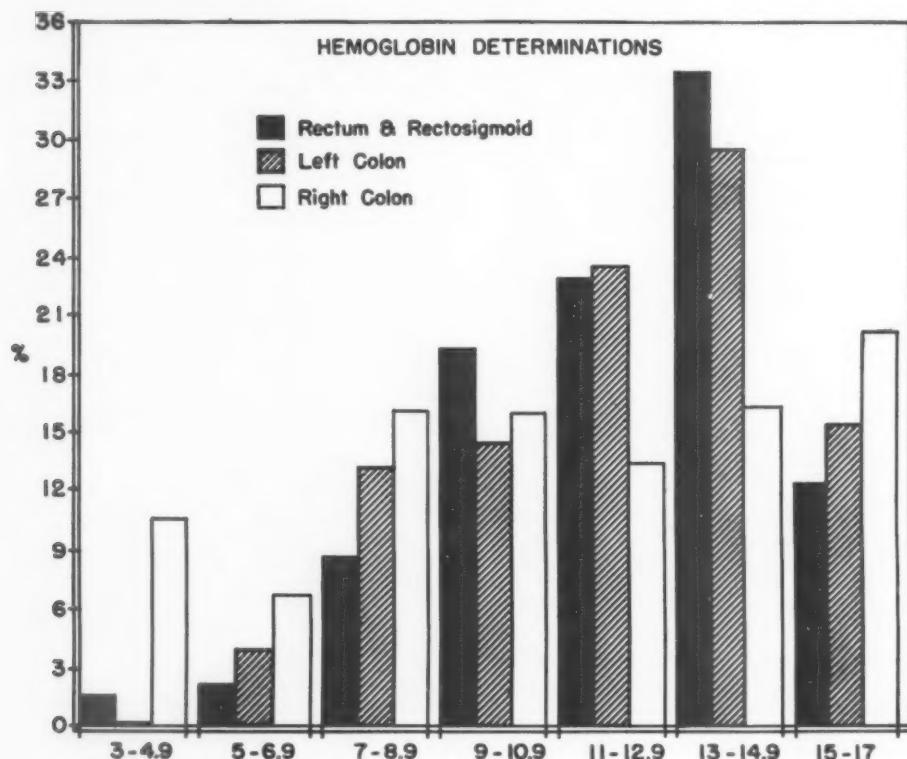


FIG. 1.—Hemoglobin determinations.

urinalysis. The hemoglobin determinations (Sahli) are shown in Figure 1. The anemia was more severe in lesions of the right colon. The percentage of patients who had less than 9.0 Gm. of hemoglobin was 13 per cent for rectum and rectosigmoid, 17 per cent for left colon, and 34 per cent for right colon. Stool examination for occult blood was nearly always positive when done. Of 212 patients who had lesions of the rectosigmoid or colon, the stool was positive for occult blood in 78 of the 92 examined.

The radiologic findings were positive by barium enema in 81 per cent of right colon lesions and 88 per cent of left colon lesions. Of the 99 patients with right colon lesions 37 showed some degree of obstruction and 44 an irregularity or other alteration which was either diagnostic or highly suggestive of malign-

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nancy. Of the 84 lesions of the left colon, 21 showed some degree of obstruction and 53 an irregularity. The majority of the remaining patients did not have barium enema visualization of the colon, usually because of complete obstruction or obvious diagnosis. In non-obstructing lesions of the rectum and rectosigmoid, barium enema was given to rule out a second lesion in the colon.

TABLE IX.—*Examination of Abdomen, Positive Findings.*

	Rectum and Rectosigmoid	Left Colon	Right Colon
Tenderness.....	31 (12%)	26 (26%)	18 (21%)
Distention.....	34 (13%)	28 (28%)	13 (15%)
Palpable mass.....	17 (7%)	35 (35%)	58 (69%)

TABLE X.—*Operative Procedures in 316 Patients.*

	R	RS	S	DC	SF	TC	HF	AC	C
Palliative:									
Colostomy.....	53	5	14	1	2	1
Ileostomy.....	8
By-pass.....	1	1	2	2
Resection.....	2	1	5	1	1	..
Exploration only.....	6	3	3	4	..	1	1	1	7
Preliminary:									
Colostomy.....	8	2	7	3	1
Cecostomy.....	1	4
Definitive:									
Resection and anastomosis...	1	3	13	6	4	2	10	10	20
Exteriorization.....	..	2	15	5	1	3
Combined resection.....	72	6	2	1
Miscellaneous.....	5	1	1

TABLE XI.—*Resectability in 441 Patients, Determined by Percentage of Total Patients, Patients Admitted and Patients Operated Upon.*

	R	RS	S	DC	SF	TC	HF	AC	C
Total patients.....	34.1	41.4	49.2	60.0	62.5	62.5	58.8	43.5	45.5
Patients admitted.....	40.4	42.9	50.8	60.0	62.5	62.5	58.8	45.5	48.8
Patients operated.....	54.5	54.5	56.4	63.1	62.5	62.5	76.8	83.3	55.5

COURSE OF PATIENTS

Three hundred and ninety-eight of the 441 patients were admitted to the hospital. Of the 43 patients not admitted, 16 elected to go elsewhere for treatment, ten refused admission, eight asked for deferred admission but did not return, and two came for irradiation therapy only. Seven patients were obviously inoperable and were sent home for terminal care.

Three hundred and sixteen of the 398 patients who were admitted had a total of 335 major operations (closure of colostomy not included). The course of the 82 patients not operated upon was as follows: Twenty-six patients were inoperable and were discharged (colostomy not indicated), and ten were inoperable and died in the hospital. The two most frequent causes of inoperability were a fixed lesion with frozen pelvis and a large nodular liver.

Operation was not performed in six patients because of severe cardiovascular disease. Thirty-three patients refused operation and four patients were given irradiation only. Three patients thought to be operable died prior to operation, two of urinary tract infection (not due to obstruction by tumor), and one of peritonitis following perforation of the malignancy.

PREOPERATIVE CARE

The most important factors determining preoperative procedures were: (1) degree of obstruction, (2) alterations of nutrition and chemical balance,

TABLE XII.—*Lymph Node Metastases in Resected Lesions. The questionable nodes were those not mentioned in the pathologic report, or not available for study as in the limited rectal tumor resections.*

	R	RS	S	DC	SF	TC	HF	AC	C
Nodes positive.....	23	4	8	2	1	0	1	3	6
Nodes negative.....	28	5	13	5	3	4	4	3	8
Nodes questionable.....	27	3	10	5	1	1	5	4	6

TABLE XIII.—*Postoperative Deaths Which Followed Exploration or Palliative Procedure.*

No.	Year	Site	Age Sex	Operation	Cause	P.O. Day	Autopsy
1.	1939	R	66-M	Colostomy	Peritonitis	20	No
2.	1940	R	22-M	Colostomy	Shock and infection	3	No
3.	1941	R	83-F	Colostomy	Widespread metastases	6	Yes
4.	1942	R	73-M	Colostomy	Cardiac failure	19	No
5.	1943	R	68-F	Colostomy	Pulmonary embolus	8	No
6.	1943	R	40-F	Exploration	Peritonitis	2	Yes
7.	1944	R	60-M	Colostomy	Cerebral vascular accident	12	No
8.	1937	RS	50-F	Cecostomy	Obstruction and chem. imbal.	26	No
9.	1937	RS	65-M	Combined			
				Resection	Peritonitis	10	No
10.	1935	S	42-M	Resection	Pneumonia	8	No
11.	1942	S	40-F	Exploration	Hepato-Renal syndrome	32	No
12.	1938	DC	42-M	Resection	Peritonitis	17	Yes
13.	1941	DC	71-M	Exploration	Pneumonia	10	No
14.	1944	DC	67-F	Exploration	Obstruction	50	No
15.	1934	TC	66-M	Ileocolostomy	Pneumonia	2	No
16.	1940	HF	43-M	Ileocolostomy	Peritonitis	9	Yes
17.	1934	C	23-M	Ileocolostomy	Peritonitis	37	Yes
18.	1936	C	47-M	Ileocolostomy	Peritonitis	17	No
19.	1939	C	61-M	Ileocolostomy	Widespread metastases	14	Yes
20.	1943	C	38-F	Exploration	Shock and hemorrhage	1	Yes

and (3) concurrent disease. The treatment of the intestinal obstruction depended on its severity. Whereas most patients on a low residue intake were adequately decompressed by repeated enemas with or without the aid of a Miller-Abbott tube, some required a cecostomy or colostomy. The attainment and maintenance of an empty bowel both preoperatively and postoperatively was considered the most important single factor in the recovery of these patients. A sulfonamide, usually sulfasuxidine, was routinely employed for several days before operation and penicillin was administered for 48 hours preoperatively after these preparations were available. Streptomycin was not

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given to any patient in the group under consideration. Alterations in fluid and electrolyte balance, hypoproteinemia, vitamin deficiency, and anemia were ascertained by history, physical and laboratory findings, and corrected by appropriate measures.

TABLE XIV.—*Postoperative Deaths Following Preliminary Colostomy for Obstruction.*

No.	Year	Site	Age		Operation	Cause	P. O.	
			Sex	Day			Autopsy	
1.	1936	R	39-M		Colostomy	Peritonitis	12	No
2.	1938	R	48-M		Colostomy	Peritonitis	8	No
3.	1940	R	62-F		Colostomy	Peritonitis	3	No
4.	1942	R	52-M		Colostomy	Uremia	4	No
5.	1932	RS	25-M		Colostomy	Pneumonia	10	No
6.	1941	S	55-F		Colostomy	Peritonitis	4	Yes
7.	1944	S	73-F		Colostomy	Pulmonary embolus	11	No
8.	1944	DC	80-F		Colostomy	Cardiac failure	8	No

TABLE XV.—*Postoperative Deaths Following Resections. Operations abbreviated as follows: Abd-per.—combined abdominoperineal resection, Obs-res.—obstructive resection, Res.-ana—resection and primary anastomosis, and Rt.-col.—right colon resection with ileotransverse colostomy.*

No.	Year	Site	Age		Operation	Cause	P. O.	
			Sex	Day			Autopsy	
1.	1933	R	62-F		Abd-per.	Peritonitis	14	No
2.	1937	R	58-M		Abd-per.	Peritonitis	6	Yes
3.	1937	R	68-M		Abd-per.	Pneumonia	11	No
4.	1941	R	53-M		Abd-per.	Pulmonary embolus	5	Yes
5.	1941	R	50-M		Abd-per.	Peritonitis	12	No
6.	1942	R	68-M		Abd-per.	Uremia	4	No
7.	1943	R	54-F		Abd-per.	Pulmonary embolus	1	No
8.	1943	R	70-M		Abd-per.	Cerebral vascular accident	3	Yes
9.	1943	R	64-M		Abd-per.	Cardiac failure	4	No
10.	1943	R	50-F		Abd-per.	Hemorrhage and shock	3	No
11.	1944	R	68-F		Abd-per.	Cardiac failure	5	No
12.	1944	R	60-M		Abd-per.	Pneumonia	8	No
13.	1934	RS	62-F		Abd-per.	Cerebral vascular accident	2	No
14.	1939	RS	52-M		Coffey	Peritonitis	3	Yes
15.	1940	RS	75-M		Abd-per.	Cerebral vascular accident	6	No
16.	1933	S	55-F		Obs-res.	Peritonitis	5	Yes
17.	1934	S	63-F		Obs-res.	Obstruction and chem. imbal.	11	Yes
18.	1938	S	26-M		Obs-res.	Pneumonia	6	No
19.	1939	S	64-M		Obs-res.	Pneumonia	10	Yes
20.	1941	S	47-M		Obs-res.	Peritonitis	11	Yes
21.	1945	S	61-M		Obs-res.	Peritonitis	11	No
22.	1938	DC	65-M		Obs-res.	Chemical imbalance	17	No
23.	1944	DC	83-F		Res.-ana.	Cardiac failure	6	Yes
24.	1934	SF	63-M		Res.-ana.	Peritonitis	8	Yes
25.	1944	TC	71-F		Res.-ana.	Shock following plasma	5	No
26.	1933	C	54-M		Rt.-col.	Pneumonia	11	No
27.	1935	C	64-F		Rt. col.	Hemorrhage and shock	1	No
28.	1936	C	67-M		Rt.-col.	Peritonitis	9	No
29.	1941	C	75-F		Rt.-col.	Pulmonary embolus	29	Yes

OPERATIONS

The various surgical procedures carried out are shown in Table X. Exploration alone and various palliative procedures were performed in 126 patients. The majority of these patients had a colostomy. Ileotransverse colostomy was

performed in 13, palliative resection in ten, and colocolostomy in one. Points of invasion and metastases either alone or in combination in these 126 patients were as follows: Invasion of pelvic or abdominal wall, 54; metastases to liver, 38; invasion of the urinary bladder, 31; peritoneal implants, 26; abdominal carcinomatosis, 14; periaortic lymph node enlargement, 11; and invasion of small bowel, 6. Although liver metastases or bladder invasion did not necessarily contraindicate resection, hope for cure could obviously not be held. Preliminary decompressing operations were performed in 26 patients, usually as an emergency procedure, prior to a later attempt to resect the lesion.

Operations which justified a reasonable hope for cure are shown in Table X under definitive procedures. The combined resections were the one-stage combined abdominoperineal resection (the Miles procedure). Of the miscel-

TABLE XVI.—Summary of Postoperative Mortality.

	Palliative Operations	Postoperative Deaths	Preliminary Operations	Postoperative Deaths	Resections	Deaths
R	61	7 (11%)	8	4 (50%)	78	12 (15%)
RS	9	2 (22%)	2	1 (50%)	12	3 (25%)
S	22	2 (9%)	8	2 (25%)	31	6 (19%)
DC	7	3 (43%)	7	1 (14%)	12	2 (17%)
SF	3	0	1	0	5	1 (20%)
TC	3	1 (33%)	5	1 (20%)
HF	3	1 (33%)	10	0
AC	2	0	10	0
C	16	4 (25%)	20	4 (20%)
Total	126	20 (15.9%)	25	8 (30.8%)	183	29 (15.8%)

TABLE XVII.—Postoperative Mortality During the Three Periods from 1931 to 1945.

	Palliative Operations	Mortality	Preliminary Operations	Mortality	Resections	Mortality
1931-35	21	14%	3	33%	22	32%
1936-40	50	16%	11	27%	51	16%
1941-45	55	16%	12	33%	110	13%

laneous procedures, two had local excision of rectal lesions as they refused more extensive resection. One had preliminary colostomy followed by resection and anastomosis through a posterior perineal approach. Two others had preliminary colostomy followed by perineal resection of the rectal lesion, and implantation of the distal loop into the vagina. One rectosigmoid lesion was removed by a modified Coffey procedure. One patient with polyposis and malignant change in the sigmoid had a resection from mid-transverse colon to lower sigmoid. The proximal loop was brought out as a colostomy and the distal loop turned in.

The resections for lesions of the hepatic flexure, ascending colon and cecum extended from the terminal ileum to transverse colon, continuity being re-established by ileotransverse colostomy. For lesions of the transverse colon, splenic flexure, descending colon and sigmoid, primary resection and anastomosis and

exteriorization procedures were employed in about the same number of patients. More recently, however, primary resection and anastomosis was usually performed. A closed two-layer anastomosis with silk was commonly employed. Open anastomosis was infrequently carried out.

In a number of patients, resection of adjacent structures was necessary because of tumor invasion. These included small bowel, stomach, abdominal wall, gallbladder, ureter, urinary bladder, vas deferens, uterus, tubes, and ovaries. Among the unusual operative findings, four cases merit comment. In three patients, two with sigmoid and one with cecal carcinomas, intussusception was present. The fourth patient had an adenocarcinoma of the cecum which had caused obstruction at the ileocecal valve. This had been partially relieved by a spontaneous ileocolic fistula.

TABLE XVIII.—*The Results in 126 Palliative Operations. Average survival and survival range in months.*

	Total Operations	Died in Hospital	Lost to Follow-up	Total Followed	Living	Dead	Average Survival	Survival Range
R	61	7	1	53	1	52	13	1-80
RS	9	2	0	7	1	6	11	2-33
S	22	2	1	19	1	18	7	2-25
DC	7	3	0	4	0	4	7	1-14
SF	3	0	0	3	0	3	6	1-15
TC	3	1	0	2	0	2	12	2-23
HF	3	1	0	2	0	2	5	3-7
AC	2	0	0	2	0	2	7	2-13
C	16	4	0	12	0	12	4	1-13

RESECTABILITY

In Table XI are shown the percentage of patients in whom the lesion was resected with reasonable hope of cure. Preliminary decompressing operations were omitted from the calculations. Resectability may be expressed as percentage of patients seen, of patients admitted to the hospital, or patients recommended for operation, or of patients subjected to operation; the latter being the most frequent form. It seems apparent that resectability expressed as percentage of resections among total patients seen would give the most comparable and accurate statistics, as this would probably represent the best index of the willingness and ability of the surgeon to extend help to the poorer risks. It might also indicate progress in early diagnosis of these lesions. By careful choice of patients, the other three expressions of resectability could be extended to high percentages, and reflect selectivity rather than resectability. For comparison, the table shows resectability computed as indicated.

Based upon the entire group, resectability was slightly higher in white than colored, and appreciably higher in the female than male. It was slightly greater in those under 60 years than those over this age.

Pathology: All the resected lesions and the inoperable tumors from which a biopsy was obtained were adenocarcinomas with four exceptions. One cecal and two rectal tumors were lymphosarcomas, and one cecal lesion was an

unclassified sarcoma. These will be considered separately in the follow-up studies. The lesions were not graded or classified. The importance of lymph node metastases is generally recognized. Unfortunately, in a substantial number of pathologic reports the presence or absence of lymph nodes was not mentioned (as noted in Table XII) thus detracting from the value of this phase of the analysis. Four squamous cell carcinomas of the anus were found during the study but were not included.

Postoperative Complications: The non-fatal complications included 13 wound infections and two wound disruptions. Ten patients developed intestinal obstruction, three had peritonitis, and one postoperative hemorrhage. Thrombo-phlebitis occurred 11 times and pulmonary embolus twice. Seven patients had atelectasis or pneumonia. Cardiac failure and unexplained pleural effusion

TABLE XIX.—*The Results in 183 Resections from 1931 to 1945 Inclusive; the Follow-up Period Closing April 1947. The living are survivors for 16 months to 17 years.*

	Total Resections	Died in Hospital	Lost to Follow-up	Total Followed	Dead	Living
R	78	12	3	63	24	39
RS	12	3	0	9	4	5
S	31	6	1	24	8	16
DC	12	2	1	9	4	5
SF	5	1	0	4	2	2
TC	5	1	0	4	3	1
HF	10	0	2	8	3	5
AC	10	0	0	10	5	5
C	20	4	1	15	5	10

TABLE XX.—*The Five Year Survivals for Resections Performed 1931 Through 1940.*

	Total Resections	Died in Hospital	5 Year Survivors		
			Living	Dead	%
R	26	3	11	4	57.7
RS	8	3	3	0	37.5
S	10	4	5	0	50.0
DC	7	2	2	0	28.6
SF	4	1	1	0	25.0
TC	2	0	1	0	50.0
HF	5	0	1	1	40.0
AC	6	0	1	0	16.6
C	9	3	3	0	33.3

were present once each. Parotitis occurred in three patients. Two patients had a perineal urinary fistula, and one had persistent though not incapacitating urinary difficulty because of an atonic bladder following combined abdomino-perineal resection. Urinary bladder disturbance and infection were fairly frequent in minor degree and were not tabulated. Cerebral vascular accident occurred twice. Two transfusion reactions were recorded. One patient, admitted because of thyrotoxicosis, suddenly became obstructed completely by a previously asymptomatic carcinoma of the transverse colon. Thyroid crises followed operation for the carcinoma but responded to treatment after four days.

OPERATIVE DEATHS

Included in this group are all deaths which occurred in the hospital at or following operation. Tables XIII to XVII summarize all these deaths so that only brief comment is necessary.

Of considerable interest are the deaths due to peritonitis, which caused 35 per cent of the postoperative mortality. Four instances of peritonitis were due to leak at the suture line; in six the bowel was entered with gross soiling during the procedure; in another six, leakage and intraperitoneal soiling occurred at the site of the colostomy; and in four, various other causes resulted in the infection. Four of these deaths followed preliminary colostomy for obstruction, and two followed attempted exteriorization for sigmoid lesions performed in the presence of marked distention.

It seems apparent from these deaths that the following principles should be re-emphasized. First, a satisfactory anastomosis cannot be performed if certain cardinal points are not observed, *i.e.*, adequate blood supply, absence of tension, non-strangulating sutures, accurate approximation, and preoperative decompression of the bowel. Second, meticulous dissection must be carried out to avoid entering the bowel, particularly in the presence of marked inflammatory reaction. Third, an adequate blood supply is as necessary to both loops of a colostomy as to the anastomosed limbs of bowel. Fourth, parietal peritoneum and bowel wall cannot be sutured to hold up a colostomy loop without danger, and the colostomy loop should not be under tension. Fifth, definitive surgery should not be attempted in the presence of distention.

The mortality rate in 78 one-stage combined abdominoperineal resections for tumors of the rectum and rectosigmoid was 17.9 per cent; in 26 exteriorizations (obstructive resections) for lesions of segments from the transverse colon to the rectosigmoid, 29.6 per cent; in 28 resections with primary anastomosis in the same sites 10.7 per cent; and in 40 right colon resections for lesions of the cecum, ascending colon, and hepatic flexure, 10.0 per cent.

RESULTS

In the follow-up studies, deaths were due to the malignancy unless otherwise noted. The living who had resections were without known recurrence unless so stated. The results following palliative operations are shown in Table XVIII. One patient with a carcinoma of the rectum was still living after 18 months; one with a rectosigmoid lesion, 16 months; and one with a sigmoid tumor, 27 months.

The results in 183 definitive resections are shown in Table XIX. Three patients with rectal lesions died of other disease; one of melanosarcoma, one of cerebrovascular accident and one of unknown cause. Of the patients who had resection for sigmoid tumors, one died of pneumonia and streptococcal empyema, and one patient was living with recurrence. In the hepatic flexure group, one died 13 years and seven months after resection, the cause was an undifferentiated carcinoma of the kidney; and the patient had a radical mastectomy for carcinoma of the breast in the interim. Two other patients in this

group were living with recurrence. One of the patients who had an ascending colon lesion was readmitted three years after resection with intestinal obstruction. He failed to respond to nonoperative measures, and at exploration no cause for the obstruction and no recurrence could be found. His symptoms subsided rapidly after operation, but he expired, apparently of a pulmonary embolus. No autopsy could be obtained. Two patients died of other causes following resection for carcinoma of the cecum; one of a coronary occlusion one month after discharge, and one of a malignancy of the tonsil two years later. The two patients with lymphosarcoma of the rectum were not operated upon. One died preoperatively of urinary tract infection and uremia. The other was given irradiation therapy and died of a cerebrovascular accident 33 months later. The patient with lymphosarcoma of the cecum was living 10 years after resection, and the patient with the unclassified sarcoma of the cecum was living four and one-half years after operation.

CONCLUSIONS

1. Early diagnosis of malignant lesions of the colon and rectum is one of the most important factors in increasing resectability. Such early diagnosis depends primarily on adequate investigation, mainly by simple, readily available means, when suspicious symptoms such as change in stool or bowel habit and abdominal pain are encountered.
2. Intestinal obstruction is a complicating factor requiring careful consideration and individualized treatment.
3. Appropriate measures must be utilized preoperatively to correct fluid and electrolyte balance, hypoproteinemia, vitamin deficiency, and anemia.
4. Improved surgical technic, blood replacement at operation, better anesthesia, the antibiotic and chemotherapeutic agents and gastro-intestinal intubation are advances in treatment which have decreased morbidity and mortality.
5. Resection and primary anastomosis for lesions of the colon, and combined abdominoperineal resection for tumors of the rectum are at present the procedures of choice at this hospital.

Note: The author wishes to express his gratitude to Dr. Deryl Hart for his help and encouragement during this study.

THE MANAGEMENT OF MASSIVE GASTRODUODENAL HEMORRHAGE*

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THE TERM MASSIVE HEMORRHAGE implies rapidly progressive exsanguination and if its use were restricted to the description of a very specific clinical picture, much of the confusion and conflict of ideas on the subject might be avoided.

Hemorrhages from gastric or duodenal ulcer are commonly mild or moderate in severity and, in most instances, produce melena without hematemesis. Two ounces of blood are sufficient to produce a tarry stool.⁹ Yet a pint of blood may be lost into the intestine over a period of several hours without producing any clinical symptoms whatever. The designation "Massive Hemorrhage," however, should be applied to a rapid loss of blood of such proportions as to cause unmistakable hemorrhage shock.

PATHOLOGY

Gastric, duodenal, and anastomotic ulcer are responsible for approximately 85 per cent of the gross hemorrhages from the upper digestive tract.^{5,10} The fatal type of bleeding usually originates in a posterior penetrating duodenal ulcer or a penetrating ulcer of the lesser curvature of the stomach. While persistent slow bleeding generally comes from an erosion of the smaller arteries and veins of the submucosal plexus, massive hemorrhage is invariably arterial in origin and follows erosion of vessels of large calibre, usually the superior pancreaticoduodenal or the right or left gastric arteries or their major branches. In the base of the ulcer crater, as exposed at operation or autopsy, one finds the eroded stoma of a thickened sclerotic artery. It may be partly or completely occluded by a clot. Fixed in surrounding dense scar tissue the eroded vessel cannot retract, thus defeating nature's most efficient mechanism for arterial hemostasis. As the occluding clot is digested or dislodged, the bleeding recurs. Occasionally no ulcer is found in the specimen and the source of bleeding may be invisible to the naked eye. In two of our cases the bleeding vessel, without any gross ulceration, was found concealed between adjacent folds of mucous membrane. Heuer¹⁵ reported a fatal case in which the pathologist, failing to find any erosion of the mucosa of the stomach or duodenum, injected the gastric artery with saline from a pressure bottle and observed a jet of fluid from the mucosal lining. Serial sections of the area showed a small ruptured aneurysm concealed by overlying mucosal folds.

The effects of severe acute anemia and sustained hypotension upon various organs and tissues are well known but deserving of comment, and are worthy

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of more emphasis than they have received. The *immediate* effect of a rapid diminution in blood volume and hypotension may be acute circulatory failure or acute forward failure of the heart. When the blood pressure falls below a certain critical level the vasoconstrictor center, suffering from impaired blood supply, becomes weakened and loses its tone, resulting in further decline in blood pressure. The medullary centers may become irreparably damaged as a result of inadequate nutrition. *Prolonged hypotension* with qualitative as well as quantitative alterations in the circulating blood will produce changes of a serious nature in all of the vital organs. Cerebral anemia leads to cerebral anoxia, manifested by stupor, dulling of the sensorium, and coma. Convulsions may be observed and a bilateral or unilateral Babinski sign may be found. Damage to the heart is indicated by the development of embryocardia or gallop rhythm with rapid appearance of pulmonary edema and death. The patient may complain of anginal pain, the result of acute coronary insufficiency, and such insufficiency may result in localized areas of necrosis or even gross myocardial infarction. The prolonged fall in blood pressure leads to diminished glomerular filtration with oliguria, anuria, rise in blood urea nitrogen and non-protein nitrogen, albuminuria, cylindruria and hematuria. Disturbances in the acid base balance of the blood may occur with hyponatremia, hypochloremia, and increased serum potassium and carbon dioxide combining power.

It is well known that severe gastroenteric bleeding produces a marked elevation of the blood urea nitrogen in eight to ten hours. Clinical observations and recent experimental investigations¹³ have shed much light on the pathogenesis of this biochemical change. The anemia *per se* does not seem to be a factor. Most important are the absorption of digested blood proteins and the prolonged fall in blood pressure. Either of these factors alone will produce an appreciable elevation but the combined effect of both will result in a higher azotemia of longer duration. Knowledge of the degree of azotemia in gastroenteric hemorrhage is of valuable clinical help since a sustained rise in blood urea nitrogen, in the absence of severe dehydration or pre-existing kidney pathology, is usually indicative of persistent bleeding. The blood urea nitrogen remains elevated for only 24 to 36 hours following one episode of bleeding. It has been shown experimentally¹⁹ and observed clinically⁸ that marked hyperazotemia with symptoms resembling uremia may follow sustained hypotension in severe gastro-intestinal hemorrhage and may terminate fatally. We have one instance of this among our fatal cases. A blood urea nitrogen above 100 milligrams is a very serious prognostic sign.²⁰

MORTALITY

A patient with massive gastroduodenal hemorrhage gives a history of sudden weakness, dizziness, or syncope followed immediately and almost invariably by vomiting of a large amount of blood, sometimes a loose tarry stool, but often both. He is pale, cold and sweating, slightly cyanotic, restless and complaining of thirst. The pulse is small and rapid, often above 120, the systolic pressure below 90. Blood counts and hemoglobin estimations are low

though not necessarily an accurate index of the magnitude of blood loss at this stage, but clinical evaluation indicates an alarming acute anemia.

With a picture so precise and so characteristic one should expect a reasonable conformity in recorded mortality risks. Yet, a review of a large number of reports concerned with both medical and surgical management reveals variations in mortality from 1 to 40 per cent. The discrepancy must indicate that the authors were reporting series of cases which were not comparable. Gross hemorrhage of mild degree has often been placed in the same category with massive hemorrhage. Many reports make no attempt to segregate patients into age groups and yet age, as will be shown later, is a most important prognostic factor. Combined reports of operative and non-operative management often fail to mention the stage at which surgery was performed or the type of operative procedure employed. Many reports on expectant treatment exclude from their tables the deaths following operations performed after prolonged conservative management had failed to stop bleeding. Institutions differ in the type of clinical material admitted, a hospital with an emergency ambulance service obviously received a higher proportion of the severer hemorrhages. Hospital mortality figures, of course, do not include patients who succumb to bleeding at home, and they will occasionally exclude the patient who succumbs in the emergency room before actual admission to the ward is effected.

Hematemesis is almost a constant finding in acute exsanguinating hemorrhage from penetrating duodenal ulcer and, as conceded by Meulengracht,¹⁸ is of far more serious prognostic importance than melena. Yet, in a recent analysis by Eads,¹⁰ reporting a mortality of 2.3 per cent in 129 patients treated medically for massive gastro-intestinal bleeding, there are included 94 duodenal ulcer patients, only four of whom vomited blood. A low hemoglobin and erythrocyte count certainly mean bleeding of significant proportions, but they are not necessarily indicative of hemorrhage of the acute profuse type which the term massive implies and in which there is an immediate threat to life.

Evaluation of the statistics which appear in the literature is consequently discouraging and difficult and unless reports are subjected to a most critical analysis erroneous and dangerous deductions may easily be made. However, there seem to be several significant observations on which there is more or less general agreement.

The mortality risk of hemorrhage from ulcer increases with the age of the patient. In individuals under 45 years of age the risk is obviously smaller though perhaps not nearly as slight as some reports imply. Bohrer⁴ analyzed 548 carefully documented cases of severe acute bleeding treated conservatively, all patients having a hemoglobin of 35 per cent or less and a red cell count of 2 million or less. The combined mortality of all age groups was 16.7 per cent. Bleeding gastric ulcer above age 45 showed a mortality of 28.7 per cent; below the age of 45 the risk was 20 per cent. Bleeding duodenal ulcer was fatal in 22 per cent above age 45, and in 6 per cent below age 45. This last figure, 6 per cent, is difficult to reconcile with the widespread belief that the risk to life of hemorrhage from ulcer in the younger group is negligible.

Hanson and Pederson¹⁴ found that of 393 patients with fatal hematemesis and melena in Copenhagen hospitals during the period 1915-1937, 13 per cent were under 40 years of age. Heuer,¹⁵ in analyzing the reviews of Holman, Clifton, and Cooper, all of the New York Hospital, estimates that of 337 patients admitted for severe bleeding 15 per cent were examples of fatal hemorrhage. In the older age group Blackford and Williams,² Allen and Benedict,¹ Chiesman⁶ and others, report a mortality of 25 to 33 per cent. Jankelson and Segal¹⁶ found the average age of those with fatal bleeding ulcer was 54 years. In Meulengracht's recent report¹⁸ he describes 26 fatalities and points out that 25 of the 26 patients were over 40 years of age and over half of those were over 60. Welch and Yunich²² report 125 patients with ulcer hemorrhage treated by a standard medical routine. One third had bled mildly and two thirds severely. In the group under 50 years of age the mortality was 1.3 per cent. Twenty per cent of those over 50 died.

Allen¹ reported that 60 per cent of the deaths in his group followed the first hemorrhage, and in Blackford's series² 78 per cent of all fatalities occurred with the first bleeding episode.

That recurring bleeding is particularly ominous is borne out by almost all reports. In this connection the comments of Avery Jones,¹⁷ are well worth examining. He expresses anxiety over cases of chronic gastric ulcer who undergo recurrent hemorrhage while in the hospital and who are over 50 years of age. In this group a single recurrence of bleeding was fatal in 50 per cent; a second recurrence was fatal in 60 per cent of the patients. In Chiesman's⁶ group of 191 patients, the mortality among 129 who bled only one day was 1.5 per cent while among 62 who bled 48 hours or longer the death rate was 74 per cent.

Although the mortality rate in general has been somewhat lower in females than in males of the same age group^{2, 5, 22} the risk is still great enough to caution against undue optimism in the treatment of serious hemorrhage in women.

The literature discloses only a small number of contributions from which one might evaluate the risk of surgical intervention in massive gastroduodenal bleeding. The statistical results deal in many instances with a definite type of case: the patient whose condition deteriorated steadily for many days and upon whom surgery was undertaken as a last resort. The outlook following exploration under such circumstances is too well known to require much comment. Walters²¹ states that "operative treatment in the terminal stages has proved relatively hopeless." Heuer¹⁵ reported a mortality of 70 per cent for operation after 48 hours of hemorrhage, and 10 per cent for early cases. Finsterer¹¹ reports a mortality of 29.7 per cent following surgery after 48 hours or more of hemorrhage as opposed to a 5 per cent death rate for early operation. It is only fair to note however that Finsterer's early cases included many patients who had hemorrhage of mild or moderate degree and who might have ceased bleeding under expectant treatment. This may also be true of the group of 200 patients reported by Bohamansson³ who were oper-

MASSIVE GASTRODUODENAL HEMORRHAGE

ated upon during the acute stage of hemorrhage with a postoperative mortality of 5.2 per cent. Gordon-Taylor,¹² during the period 1933 to 1939, operated upon 18 early cases, many within 24 hours of the onset of bleeding, with one death, a mortality of 5.5 per cent. During the same period late operation upon seven patients was followed by four deaths, a mortality of 59 per cent.

It is obvious that little may be gained by contrasting the statistics of the proponents of medical management with the figures on surgical mortality. The groups reported, to date, at least, are not strictly comparable. The surgeon, summoned when (according to a recent report on the success of expectant treatment) "the patient is responding poorly to medical management and a fatal outcome appears likely"¹⁰ has little to start with. His results should be reported, under those conditions, not as mortality rate but in terms of the number of lives saved. On the other hand, the surgeon who operates immediately upon *all* bleeding patients may justly be criticized for subjecting to hazardous surgery many individuals who might have stopped bleeding spontaneously or upon whom operation might have been performed at a later date, if at all, with much less risk to life.

The following preliminary report from the Roosevelt Hospital is a summary of our more recent experience covering the years 1943 to 1947 inclusive, with a presentation of a plan of management and the criteria for operation.

During the five-year period from 1943 to 1947 there have been admitted to the Roosevelt Hospital 120 patients with massive gastroduodenal hemorrhage. The diagnosis of ulcer was established in 107 of these patients. In the remaining 13, an ulcer was strongly suspected but could not be proven roentgenologically.

Eighty-four of these patients were treated expectantly, and among these there were 13 deaths (15 per cent). Fifty-eight patients in this group of 84 were over 45 years of age and all but two of the fatalities were in this older group. Massive hemorrhage, treated expectantly, therefore, showed a mortality of 19 per cent in patients over 45 years old.

Eleven patients in whom bleeding appeared uncontrollable were operated upon within 48 hours of admission, with one postoperative fatality (9 per cent).

The remaining 25 patients treated surgically form a group which is too heterogeneous for accurate analysis. Operations in this group were done between the third and twenty-first day after admission. The great majority had stopped bleeding with expectant treatment and operation was performed as an elective procedure, but in three instances in which surgery was employed only as a last resort in patients who had not responded to prolonged conservative treatment, the outcome was fatal. One of these three patients had received over 10,000 cc. of blood preoperatively, during a period of 12 days of expectant treatment.

Our plan of management is predicated upon the following beliefs and applies only to massive exsanguinating hemorrhage as above defined.

1. Indiscriminate emergency surgery for ulcer hemorrhage should be strongly condemned. With the few exceptions noted below, massiveness of the

hemorrhage does not constitute an indication for operation without a preliminary trial of restorative measures and expectant treatment.

2. Despite the impressive reduction in mortality in recent years as a result of improved medical management, a certain percentage of patients will continue to die of uncontrollable ulcer hemorrhage.

3. The risk of lethal hemorrhage in younger patients is relatively small and emergency operative intervention in this group will not often be necessary. The patient under 45 not only tolerates the effects of critical acute anemia better than the older patient, but his ulcer being often of fewer years' duration, shows less penetration and fibrosis and is thus more likely to cease bleeding spontaneously.

4. All serious bleeders above the age of 45 are potential candidates for emergency operation and should be seen and followed jointly by the internist and the surgeon from the moment of admission to the hospital. The older the patient in this group, the greater the risk to life from massive bleeding.

5. Severe ulcer pain preceding the hemorrhage, or persisting after the hemorrhage, is a serious symptom^{7, 12} usually indicating deep penetration, or impending or localized perforation.

6. In the presence of pyloric stenosis hemorrhage is more likely to continue or recur^{11, 12} and the indication for surgery therefore becomes more urgent when such pathology is known or recognized.

7. The patient over 50 bleeding from a chronic *gastric* ulcer, is the one most likely to die of uncontrollable hemorrhage.^{12, 22}

8. Continued bleeding in the older age group may be considered of lethal proportions if the patient's blood pressure does not rise satisfactorily with repeated transfusions in the first 24 hours.

9. Surgical intervention, when indicated, carries the least risk during the first 48 hours of active bleeding.

10. In the older group recurrent severe bleeding in the patient just recovering from a previous episode is of the gravest prognostic importance.

11. As a result of the profound tissue and chemical changes induced by prolonged exsanguinating hemorrhage, particularly in the older patient, the mortality from late surgical intervention is prohibitive.

MANAGEMENT OF MASSIVE GASTRODUODENAL BLEEDING

1. Active treatment for the patient in shock is begun at once without subjecting the patient to any but the most cursory physical examination.

2. Nothing is permitted by mouth except small sips of water or cracked ice.

3. Blood replacement is begun at once. Under the most urgent conditions plasma may be employed until blood typing and cross-matching are accomplished. Plasma alone is not adequate replacement for blood.

4. Blood is drawn for hematocrit, prothrombin, and blood urea nitrogen determinations, as well as for typing and blood counts.

5. Repeated or continuous transfusion is required as long as the systolic pressure remains below 90 or the pulse over 130, or both. It is important to

bear in mind that pre-existing hypertension may modify these values. Since the blood deficiency at this stage is quantitative rather than qualitative, blood counts and hemoglobin determinations may not give an accurate picture of the severity of the hemorrhage.

6. When restorative measures have been initiated, a rapid physical examination is made and a history secured in an attempt to ascertain the most probable source of bleeding. Rupture of esophageal varices is common enough to warrant serious consideration in the differential diagnosis of bleeding ulcer. Less frequently a blood dyscrasia may be the cause of the hemorrhage.

7. In the absence of a definite history of ulcer in a patient who is bleeding uncontrollably, and in whom surgical intervention appears likely, every reasonable effort is made to establish a diagnosis. This should include examination of the esophagus, stomach, and duodenum by roentgen-ray if necessary. Though a patient in shock should not be subjected to this procedure under any circumstances, bleeding of itself does not contraindicate the ingestion of barium and early examination. The patient is placed in the horizontal position and the barium distributed, without palpation or pressure, by turning the patient slowly from side to side. This technic has been employed many times at the Roosevelt Hospital and though it has its obvious limitations, we have found it thus far to be without danger. Despite the fact that large clots in the stomach may at times make interpretation of films difficult or inaccurate, the examination has helped on many occasions to demonstrate suspected pathology which later was confirmed. We have not employed gastroscopy as a diagnostic procedure in the presence of acute bleeding.

8. If the presence of esophageal varices is definitely excluded a small calibre indwelling tube is passed through the nostril into the stomach, the stomach lavaged with saline and continuous suction applied. Thereafter the character of the aspirated material may furnish useful information regarding cessation or persistence of bleeding. The tube tends to inhibit nausea and vomiting and by continuous removal of gastric juice may prevent digestion and liquefaction of any clot which might have formed in the eroded vessel.

9. Opiates or barbiturates, or both, are given in doses adequate to control restlessness. Morphine occasionally produces nausea and should be given cautiously.

10. Blood pressure and pulse are recorded at half-hour intervals.

11. All fluid, amino acid, vitamin, sugar and salt requirements are met by intravenous infusion and transfusion during the period of profuse bleeding. The exsanguinating patient now under discussion rarely accepts or retains the type of food provided by the Meulengracht diet. When active bleeding ceases the patient is placed on a progressive ulcer diet with the addition of aluminum hydroxide if ulcer pain is present.

12. *Indications for Operation:* When causes of bleeding other than chronic ulcer have been excluded with reasonable certainty:

a. Patients over 50 years of age who continue to show a rapid pulse, drop in blood pressure, slight air hunger, and other signs of continued bleeding

despite repeated transfusions over a period of 24 hours require surgical intervention.

b. Younger patients who continue to bleed profusely and who remain at shock levels despite repeated transfusions over a period of 48 hours require surgical intervention.

c. A recurrence of massive bleeding in the older ulcer patient demands immediate operation, delayed only by the time required for urgent blood replacement. In this type of patient procrastination may be disastrous.

d. Massive hemorrhage superimposed upon a known pyloric obstruction requires surgical intervention.

e. Simultaneous hemorrhage and perforation obviously call for immediate operation.

f. Patients who are first seen after many days of severe continuous or repeated hemorrhage are extremely poor surgical risks and are best treated expectantly. In this group simple high jejunostomy under local anesthesia, for feeding purposes, may be of value.

OPERATIVE PROCEDURE

A patient suffering an exsanguinating hemorrhage is necessarily a poor risk. Operation should not be undertaken by a surgeon whose experience with gastric problems is limited. The complicated pathology in most of these cases, and especially in those patients who have had previous stomach surgery, will tax the skill and ingenuity of the most seasoned operator. If an experienced surgeon is not available it is more prudent to accept the hazard of expectant treatment.

It is difficult to justify palliative procedures such as ligation of vessels supplying the ulcer, simple suture of the bleeder in the ulcer bed, and gastroenterostomy alone. They have generally been found ineffective in controlling the hemorrhage. *With massive blood transfusion and modern anesthesia a patient who cannot be safely conditioned for major gastric surgery should not be subjected to the added risk of operation.*

Partial gastrectomy including excision of the ulcer is the procedure of choice. In penetrating duodenal ulcer it may be wiser, in particularly urgent cases, to open the duodenum immediately, control the bleeding by means of deep silk sutures, and then proceed with the gastrectomy. Occasionally when confronted with an ulcer which has burrowed deeply into the pancreas, it is more expedient to leave the base of the ulcer behind and perform the resection around it. The duodenum distal to the ulcer is then mobilized sufficiently to permit adequate closure of the stump. Routinely in such cases, using a single fine catgut suture, we have fixed a large soft rubber tube drain to the capsule of the pancreas in the region of the ulcer and duodenal stump.

When palpation of the stomach and duodenum fails to indicate the source of the bleeding we perform wide gastrotomy and duodenotomy, irrigate thoroughly with saline, and examine the duodenal and gastric cavities with great care. If an old gastroenterostomy is present the jejunal loops are inverted

into the stomach through the stoma and may be readily inspected through the gastrotomy. By employing this procedure we have found minute bleeding erosions which had been completely missed on palpation. If a source of bleeding is not found after thorough inspection of the duodenal and gastric mucosa, we feel that the stomach and duodenum should simply be closed. We have not encountered diffuse mucosal bleeding from simple acute gastritis but we question the advisability of gastric resection as recommended by some surgeons in such cases.

The greater the depletion of the patient before operation the more susceptible will he be to the postoperative complications common to all major abdominal procedures. Infection, retarded healing of suture lines, cardiac and pulmonary complications are seen more frequently than in elective surgery and are more lethal in their consequences. However, the liberal use of blood, amino acids, and plasma if necessary, added to the measures usually employed after elective gastric surgery, will help these patients tremendously in meeting the challenge of a very trying postoperative period.

It would be most distressing to permit the problem of bleeding peptic ulcer to degenerate into a feud between the internist and the surgeon. Obstinate adherence to any concept of therapy, be it medical or surgical, may result, unfortunately, in detriment to the patient. The aggressive surgeon who attacks every bleeding ulcer without careful appraisal of the indications for operation and the risk involved exposes himself to the same censure as the internist who permits fatal exsanguination in a patient to whom early surgery might have offered a reasonable prospect of survival. Mortality statistics, as has been shown, are too unreliable as a basis for an inflexible policy. The management of the bleeding patient must be individualized, and it should be a joint enterprise and a joint responsibility for an experienced internist and a competent surgeon. Only by the closest cooperation between them will it be possible to select from the large number of patients with ulcer hemorrhage, the relatively small group who might be saved by emergency surgical intervention.

SUMMARY

1. The term massive hemorrhage should be applied only to an acute, rapid loss of blood, producing hemorrhagic shock.
2. Prolonged, severe hypotension from acute hemorrhage may cause irreparable damage to vital organs, particularly in the older patient.
3. The mortality risk of hemorrhage from ulcer increases with the age of the patient, and is greater in gastric than in duodenal ulcer.
4. Hemorrhage is more dangerous when preceded or accompanied by ulcer pain, or in the presence of pyloric obstruction, and when bleeding recurs while the patient is convalescing from a previous severe episode.
5. Surgical intervention, when indicated, carries the least risk during the first 48 hours of active bleeding.
6. A plan is presented for the management of massive gastroduodenal bleeding, and the indications for emergency surgical intervention are discussed.

7. The treatment of bleeding peptic ulcer is the joint responsibility of the internist and the surgeon.

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AN EXPERIMENTAL STUDY OF ANTI PERISTALTIC JEJUNAL LOOPS*

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SINCE THE FIRST REPORT in 1935 by Whipple, Parsons and Mullins¹⁵ of a radical resection of the duodenum and head of the pancreas for carcinoma of the ampulla of Vater, numerous modifications have been tried to overcome the difficulties which followed the initial procedure. The important complication of cholangitis led Whipple¹⁶ in 1938 to anastomose the gallbladder, and later the common bile duct, to an antiperistaltic limb of jejunum created by the Roux-Y type of anastomosis. The same type of anastomosis has been used by Allen,¹ Cole³ and others for the correction of impermeable strictures of the common bile duct.

The distressing complication of cholangitis occurs even after the modified Whipple procedure has been used, and this has stimulated interest as to the mechanism. The organism most commonly mentioned as being responsible was the colon bacillus. Numerous mechanical causes have been proposed. Wangensteen¹⁴ stressed the importance of a non-patent or stenosed stoma as an important factor in the production of cholangitis following cholecystenterostomy. Very little information is available, however, on the best length of the antiperistaltic segment of bowel to be used in the Roux-Y type of anastomosis. In reviewing the many modifications of the original Whipple operation, the authors could find only the following references to the length of antiperistaltic limb of jejunum utilized. Pearse¹² initially used a six inch loop. In later cases, this was lengthened. Dennis⁵ stated that 40 centimeters of jejunal segment were used to separate the biliary from the gastric anastomosis. His patients did not experience any postoperative cholangitis, and postoperative fluoroscopy on one of his patients "showed rapid emptying of the gastric pouch with no regurgitation into the proximal jejunal loop." Cole³ stated that the antiperistaltic limb should be at least 24 inches long when utilized in common duct surgery.

Hence, it was felt that an attempt should be made to determine the optimum length of an antiperistaltic limb of bowel. Also, that a comparison should be established between antiperistaltic limbs of jejunum and loops of jejunum "defunctioned" by an enteroenterostomy as suggested by Cattell,² Cole³ and others.

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METHODS

In order to determine the extent of regurgitation in an antiperistaltic limb of small bowel, the following experiments were performed on dogs. In the first phase of the experiment, a jejunal fistula was utilized using the method of Mann and Bollman.⁸ The abdomen was opened; the ligament of Treitz identified and divided. Approximately six inches beyond the ligament, the proximal jejunum was divided and the distal end brought out through a stab wound in the abdominal wall as a permanent stoma. A Roux-Y type of enteroenterostomy was performed implanting the proximal end of the transected jejunum into the antimesenteric border of the distal end at distances of four, eight, ten, 12, 14, 16, 20 and 24 inches from the stoma. (Fig. 1.) Postoperatively all dogs were watched carefully for the loss of

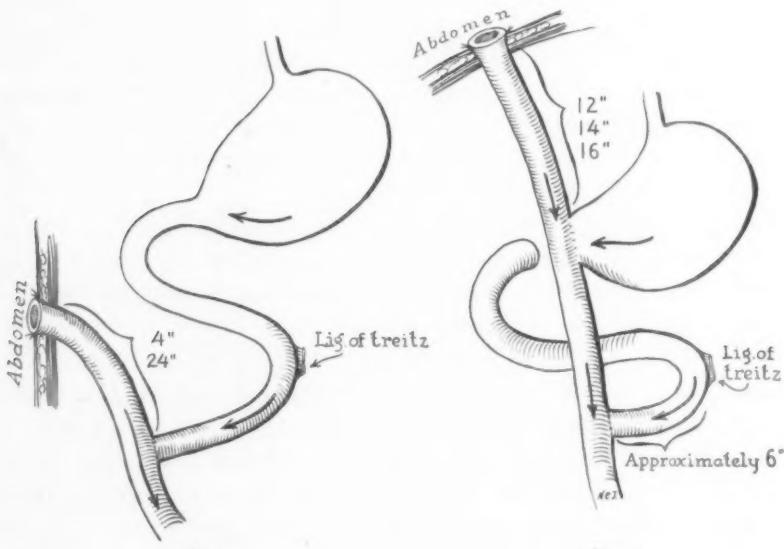


FIG. 1

FIG. 2

FIG. 1.—Jejunojejunal fistula.
FIG. 2.—Gastrojejunostomy.

intestinal secretions through the stoma. Dye, in the form of methylene blue 0.24 Gm., was given orally and staining of the stoma recorded. In addition, some dogs were studied fluoroscopically following the administration of barium by gavage without sedation or anaesthesia.

In the second phase of the experiment, the abdomen was opened and the ligament of Treitz identified and cut. Approximately six inches beyond the ligament, the jejunum was divided, and following resection of the pyloric ring of the stomach and closure of the proximal duodenum, the distal end of the transected jejunum was brought out through a stab wound in the abdominal wall as a permanent stoma. An end-to-side gastrojejunostomy was performed,

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thus creating above the gastric anastomosis antiperistaltic limbs of jejunum of 12, 14, and 16 inch lengths. The proximal end of the transected jejunum was reimplanted into the distal segment approximately six inches below the gastric anastomosis. Figure 2 which illustrates the second procedure closely simulates that seen in Whipple's article of June, 1946¹⁸ "showing antecolic or postcolic anastomoses with an antiperistaltic limb of resected jejunum." In our experiments no biliary anastomoses were performed, nor were the pancreas and duodenum extirpated.

In the third phase of the experiment, the abdomen was opened and the ligament of Treitz identified. Approximately eight inches from the ligament an enteroenterostomy was performed, the stomata being eight centimeters in length, creating "defunctioned" loops 24, 32, and 48 inches in length. The mid point of the loops was brought out through the incision and sutured to the wall. After closing the incision, an opening was made in the bowel wall creating a permanent stoma as illustrated in Figure 3.

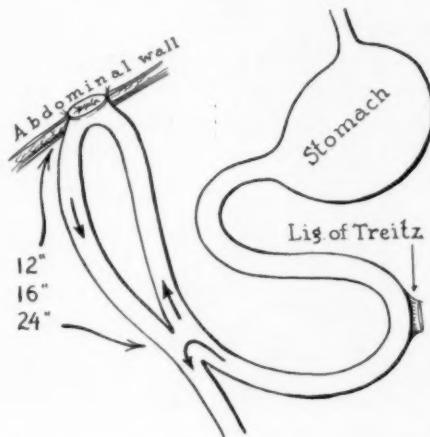


FIG. 3.—Fistula of jejunal loop "defunctioned" by a jejunoojejunostomy.

DISCUSSION

Table I summarizes the first group of experiments where variable lengths of antiperistaltic jejunal fistulae were used. It is noted that in addition to a dye given orally, the material constituting the intestinal stream will regurgitate up an antiperistaltic limb ten inches in length. Fluoroscopically, following the introduction of barium by gavage, the barium was not seen to traverse an antiperistaltic limb eight inches in length, but 15 minutes later appeared at the stoma. Observations of limbs 12 and 14 inches in length showed the barium to enter the limb readily for a distance of six inches. Postmortem examination of all of these dogs failed to reveal the presence of ulcerations in the mucosa about the stoma sites.

Table II summarizes the results in the second group of experiments where gastrojejunal antiperistaltic limbs were utilized. The minimum length of limb used was 12 inches on the basis of the previous experiment. Because of the more forceful evacuatory contractions of the stomach, it was surmised that a limb 12 inches in length would be too short. However, as noted, neither dye nor intestinal juices appeared at the stoma of a 12, 14 or 16 inch limb. Fluoroscopically, the barium entered both 12 inch limbs for a distance of five to six inches. (Fig. 4.) In one instance, the barium disappeared from the limb with the appearance of peristaltic waves. However, in the other case,

the barium persisted as a thin line despite vigorous contraction waves down the limb. Postmortem examination revealed the presence of ulcers in the 14 and 16 inch limbs in the jejunum just opposite the gastrojejunostomy stoma (Fig. 5-Fig. 6) when sacrificed 50 days and 45 days postoperatively, respectively. This closely simulates the work and findings of Mann and Williamson⁹ in one phase of their classical experiments on the production of peptic ulcers.

TABLE I.—*Antiperistaltic Jejunojejunal Fistulae*

Dog Number	Length of Antiperistaltic Limb	Presence of Intestinal Juices	Presence of Dye	Remarks
47-62	4"	Profuse brownish green in 6th postoperative day	None seen	Dog died 10 postoperative day of peritonitis.
47-65	8"	Questionable	None given	Dog sacrificed on 5th postoperative day because of distemper.
47-77	8"	Small amount of intestinal juice on 6th postoperative day	None given	Dog died on 6th postoperative day. Perforation at suture line.
47-83	8"	Scant fecal material noted	None	Given barium p. o. and fluoroscoped. 15 minutes later barium appeared at stoma. Loop lengthened to 24".
47-204	10"	Some gas and scant fecal material	Yes	Dog sacrificed 2 weeks p. o. Did poorly. Chronic bilateral glomerulonephritis and nephrosis.
47-222	10"	Slight on 6th p. o. day	None	
41-50	12"	None	None	
Short, black female cocker	12"	None	None	On fluoroscopy, barium readily entered antiperistaltic limb for distance 6". None at stoma.
47-162	14"	None	None	
40-34	16"	None	None	
41-53	20"	None	None	
47-83	24"	None	None	

Table III summarizes the results of the third group of experiments where loops of jejunum were utilized which had been "defunctioned" by means of an enteroenterostomy. Loops with 12-inch limbs were much too short. Despite a wide, patent enterostomy stoma, all of these dogs died within eight days from the time of operation. Dye and intestinal secretions literally poured out of the stomata. The deaths may be attributed to loss of fluids and electrolytes from a high fistula similar to that of a high intestinal obstruction.¹⁰ The loop with a 16 inch limb was still too short to prevent loss of intestinal juices. The loop

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FIG. 5.—Ulcer on posterior wall of jejunum opposite the gastrojejunostomy stoma.



FIG. 4.—Arrow designates anti-peristaltic limb of jejunum containing barium.

with a 24-inch limb, although it prolonged the dog's life, was unsuccessful in completely diverting the intestinal stream.

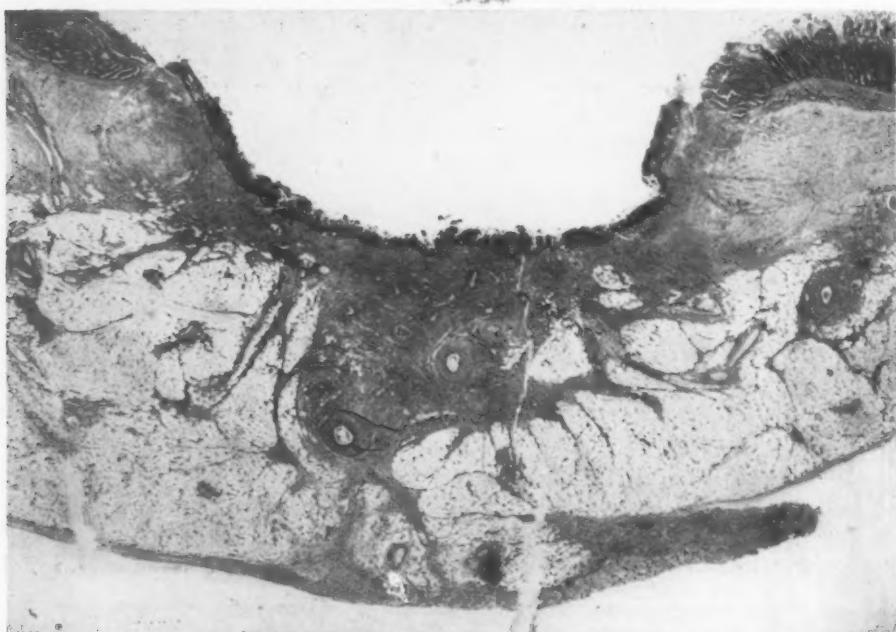


FIG. 6.—Photomicrograph of ulcer of Fig. 5. x12.5

TABLE II.—*Antiperistaltic Gastrojejunal Fistulae*

Dog Number	Length of Antiperistaltic Limb	Presence of Intestinal Juice	Presence of Dye	Remarks
48-27	12"	None	None	Fluoroscopically showed regurgitation into antiperistaltic segment for 4-5 inches. Sacrificed 78 days p. o. No ulcers noted.
48-63	12"	None	None	Barium entered limb readily for 4 inches. Sacrificed 56 days p. o. No ulcers noted.
48-5	14"			Dog died 2nd p. o. day. Acute dilatation of stomach.
47-235	14"	None	None	At post mortem ulcer noted on posterior wall of jejunum opposite gastrojejunal stoma. (50 days p. o.)
47-164	16"	None	None	Ulcer noted same as above. (45 days p. o.)

CONCLUSIONS

1. In dogs regurgitation occurred for a distance of ten inches in an antiperistaltic limb of jejunum created by a Roux-Y type of anastomosis.
2. The optimum length for the antiperistaltic limb of a Roux-Y type of

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anastomosis was found to be 12 inches. This prevented regurgitation of dye, barium or intestinal contents out of the stoma.

3. No difference was noted in the extent of regurgitation in an anti-peristaltic limb created by a jejunoojejunostomy or a gastrojejunostomy. Hence, the important factor was the length of the limb, and the force with which material entered the loop was apparently of lesser significance.

TABLE III.—"Defunctioned" Jejunal Loop Fistulae

Dog Number	Length of Ascending Limb of Loop	Presence of Intestinal Juice	Presence of Dye	Remarks
47-172	12"	Profuse	Yes	Died 7 p. o. day.
48-10	12"	Profuse	Yes	Died 8 p. o. day.
48-14	12"	Profuse	Yes	Died 7 p. o. day.
47-209	16"	Some discharge daily from stoma	Yes	Alive at end of 18th p. o. day. Sacrificed. Dye given day previously stained entire ascending loop.
48-34	24"	Slight discharge	Slight staining	

4. The use of loops longer than 12 inches in a gastrojejunral Roux-Y anastomosis resulted in peptic ulcer formation.

5. An enteroenterostomy between loops of jejunum does not short-circuit these loops. The enteroenterostomy does not divert all of the intestinal stream even when the limbs of the loops are 24 inches in length.

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SYMPATHECTOMY IN PERIPHERAL ARTERIOSCLEROSIS*†

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THE ENORMOUS TOLL taken by arteriosclerosis is still appalling and probably less progress has been made in this field than in any other in medicine. For this reason, any therapeutic method which offers the hope of staying its inexorable course should be seized upon vigorously until its possibilities have been exhausted and what it has to offer has been adequately tested and evaluated.

Considered a "degenerative" disease, arteriosclerosis has been accepted by the profession as the almost inevitable destiny of those who live long enough. It is the invariable cause of death when some intercurrent disease does not strike first. In a large number of cases it causes inestimable disability and distress long before the capital stroke is administered. In the lower extremities, obliterative vascular sclerosis is so rampant a scourge that otherwise vigorous men are incapacitated to a varying degree by it for many of the last years of their lives. From mild to disabling claudication to actual loss of one or more limbs is the terrible tribute it demands, and little has been offered to interrupt its relentless progression.

Almost universally the use of sympathectomy had been decried in the treatment of what was accepted as a progressive, organic, irreversible process. Only when angiospastic phenomena played a significant role, it was thought, could the operation help, and to use it for arteriosclerosis obliterans would serve to discredit it in the indicated situations. Yet scattered reports suggesting its usefulness in selected cases of obliterative vascular sclerosis began to appear in the literature about 1935. In that year, Harris reported good results from the procedure in 5 of 12 cases. The material included patients not tested preoperatively and those with poor responses to testing. He concluded that sympathectomy was of value in obliterative vascular disease when spasm accompanies it and that all patients showing a rise in skin temperature following block would be helped. In 1936, Lerche reported that 76.4 per cent of his sympathectomized arteriosclerotics were improved. The subject was again discussed by Atlas in 1941 in an article based upon 12 selected cases of arteriosclerosis treated by sympathectomy. All lost the sensation of cold numb feet that had been present preoperatively. Ulcers which were present in two cases healed, and intermittent claudication disappeared in seven of nine cases in which it had been present. All, preoperatively, had severe subjective and objective evidence of circulatory deficiency on an arteriosclerotic basis but by

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sympathetic block indicated that the collateral vascular pathway was capable of hypertrophy. In 1937, Pearl recommended lumbar sympathectomy in the treatment of angiospastic claudication. His conclusions were based upon the response of six cases to vaso-motor paralysis. Three of the cases showed evidence of organic arteriosclerotic disease in addition to the angiospastic phenomena. In 1942 Freeman and Montgomery reported on 12 cases with peripheral arteriosclerosis and intermittent claudication. All but one showed evidence of obliteration of the major arteries of the leg. Seven responded to sympathetic block with objective evidence of increased ability to work while three others were subjectively improved. Six of the first group were subjected to lumbar sympathectomy with immediate and persistent relief.

Trimble in 1944 published his results in 24 cases of peripheral arteriosclerosis treated by sympathectomy. Only three of the cases were not improved. These had gangrenous ulcers and came to amputation. Eight were greatly improved, the remainder moderately so. Eleven cases with ulceration or gangrene went on to complete healing. The degree of obliteration which was present is indicated by the fact that 16 had no pedal pulses, six only a faint unilateral pulse, one a faint bilateral pulse, and in one there was no record.

In March of 1946 Telford and Simmons reported on a series of 88 cases which were treated by sympathectomy. Most of these did not have preliminary testing by nerve block and hence were unselected. In 47 cases the operation was performed for severe intermittent claudication. All showed improvement although it was striking in only six which have been almost normal since operation. Not one, however, followed for five to 15 years, developed rest pain or gangrene. Forty-one cases had incipient or frank gangrene. In 21 the results were good with abolition of rest pain and a change from chronic invalidism to reasonable activity with separation and healing of the gangrenous areas. Twenty cases did come to amputation, but frequently at a lower level.

Later in 1946 de Takats gave a simple, logical rationale for the use of lumbar sympathectomy in selected cases of peripheral vascular sclerosis. Encouraged by the above reports and by the response in a case of his which preoperatively was thought to be thromboangitis obliterans but which at operation proved to be arteriosclerosis, he reversed his previous stand of recommending sympathectomy only for angiospastic states and performed the procedure in 25 selected cases of obliterative vascular sclerosis. The results were extremely good. In one group a dramatic increase in walking ability occurred, in a second amputation was averted, in a third group amputation could be performed at lower levels, while in a fourth intractable neuritic pain of the causalgic type was benefited. The rationale for the procedure was the release of normal vasomotor tonus insuring an even bloodflow uninfluenced by anything but the metabolic needs of the tissues. The sympathectomized extremity was freed from the influences of cold, of emotion, and of standing. By 1947 his series had been expanded to include 57 cases, 53 of which had

been benefited by the procedure. In discussing de Takats' 1947 paper Pearl reported that 50 arteriosclerotic extremities were improved by sympathectomy at his clinic. In about one-third of the cases the peripheral pulses showed an increase in volume or an appearance where before operation it was absent. About one-third were relieved of claudication and in many the color changes characteristic of circulatory deficiency disappeared. Not one came to amputation while in the same period of time 75 low thigh amputations were performed in a comparable series of non-sympathectomized extremities.

These encouraging reports have caused surprisingly little stir. Besides the de Takats' paper, no other article on sympathectomy for peripheral arteriosclerosis is to be found in the 1947 literature. The general attitude is still defeatist, the senescence theory still prevalent, the recommendations for treatment found in the recent literature still are primarily medical (diethyl ether,¹⁰ hypertonic saline,⁶ histidine and ascorbic acid,¹⁸ tetraethyl ammonium bromide,¹⁹ alpha tocopherol,¹⁵ etc.) It is because of this that another paper stressing the value of sympathectomy in selected cases of obliterative vascular sclerosis is not out of place. The following series, while small, is highly illustrative, and may possibly help to stimulate interest in the field.

CASE MATERIAL

Eight lumbar sympathectomies were performed upon six patients. All had advanced states of peripheral arteriosclerosis with manifestations varying from intermittent claudication to frank gangrene with or without infection. In seven instances definite benefit resulted. In one, in which gangrene had spread to beyond the middle of the foot all that was hoped for was to make possible healing of an amputation at a mid-leg level. This was achieved but of course it cannot be concluded that the sympathectomy was responsible. A summary of the cases will be given which will be followed by a more detailed discussion.

Case 1.—V. A., Sydenham Hospital No. 103854, was a 56-year-old male diabetic admitted on June 22, 1946, with a moist ulcerative gangrenous lesion about 3 by 2 inches on the dorsum of the left foot extending onto the great toe and to a lesser extent onto the other toes. The extensor tendons were exposed in the base of the ulcer. A gangrenous bleb was also present over the great toe of the other foot. Both feet were cold with dependent rubor and marked blanching on elevation. Only the right popliteal and femoral pulses were palpable. Oscillometric readings were less than 1.0 bilaterally. The histamine flare and saline absorption tests showed extremely poor collateral circulation. There seemed to be no hope for the left leg and mid-thigh amputation would have been proceeded with immediately were it not for the lesion of the right great toe which placed that limb in jeopardy as well. Because of this it was decided to employ conservative treatment until such time as the fate of the right extremity clarified. Until July 15th bed rest, wet dressings, and anti-diabetic therapy were employed. The ulcer of the left foot became larger and dirtier and the gangrenous bleb of the right great toe extended to involve most of the toe. On July 16th daily bilateral lumbar sympathetic blocks were added to the treatment. Objective and subjective warming of the members was noted which, after the first few days, persisted for progressively longer periods until after about ten days its effect lasted practically around the clock. By the 1st of August a remarkable change in the ulcer was noted; it had become clean, and was beginning to granulate and to epithelialize in from the edges. The histamine and saline absorption tests now showed

an improved collateral circulation and on the right oscilometric readings were improved. By the 21st, the ulcer was definitely smaller and both the right and left great toes were demarcating. With the ultimate successful result now almost assured, left lumbar sympathectomy was performed on August 21st. At the patient's request, because the left leg felt so much better than the right, this was followed by right lumbar sympathectomy on September 6th. By September 16th the ulcer was healed, both great toes had demarcated, and the patient had no pain, even, as was learned, when contrary to orders he walked about the ward. Of remarkable interest was that a dorsalis pedis pulse was now palpable bilaterally. The left great toe was eased off and the patient was discharged on October 11th. In December, 1946, he was readmitted for the removal of the right great toe. The left foot was healed at the time; the right went on to healing shortly after the toe had been amputated.

The patient returned to useful activity. He was readmitted in June, 1947, for a pressure ulcer of the plantar surface of the left second toe with purulent exudate extending through the toe to the dorsum. This toe was amputated with prompt healing following. There has been no further trouble of any sort since.

Case 2.—M. M., Mt. Sinai Hospital No. 553291, was a 61-year-old female diabetic admitted on August 23, 1946, with gangrene of the right great toe and severe cellulitis of the remaining toes and of the distal half of the foot. There had been a left mid-leg amputation a year before for gangrene. Marked peripheral arteriosclerosis was present with no pulses palpable in the foot. The right popliteal pulse was faintly palpable. Oscilometric readings were markedly reduced. No hope was held for the limb, but because the other had already been lost, an effort to save this one was made. Treatment consisted of bed rest, wet dressings, penicillin, and daily sympathetic blocks. The cellulitis receded and some improvement in color and increased warmth of the foot occurred. An alcohol lumbar sympathetic block was done to provide a more permanent effect. The right great toe was then amputated, leaving a dirty base containing considerable slough. Infection and gangrene extended to the remaining toes which were successively amputated. Tendon and soft tissue slough persisted in the base of the wound but no longer seemed to be spreading. The alcohol block, the effect of which was wearing off, was repeated, with return of the warming of the foot that had been obtained previously, and on two occasions the wound was debrided of accessible slough. No further extension of gangrene or infection occurred and by late November the wound was finally clean and granulating. On December 12, 1946, she was transferred to a City hospital. Here on January 9, 1947, a left lumbar sympathectomy was performed as the effects of the alcohol block had again worn off. The foot was considerably warmer after operation. Healing progressed favorably and was complete by March 15, 1947, when the patient was discharged. The stump has remained well healed since.

Case 3.—B. L., Beth David Hospital No. 46-4386, was a 65-year-old diabetic admitted with a six-month history of intermittent claudication and rest pain in the right foot. Marked obliterative vascular sclerosis was present; both feet were cold and discolored reddish-purple, the right more so than the left. Both popliteal pulses were palpable but none distal to these. Upon right sympathetic block the pain was relieved but only slight warming of the foot was obtained. Courses of etamon and of diethyl ether were given but gangrene of the third toe of the right foot developed in spite of these. The toe was amputated after demarcation had occurred but sloughing tendon was seen in the base and some cellulitis was present proximal to it. Roentgen-ray showed marked calcification of the vessels and the limb's coldness extended up to the mid-leg. Lumbar sympathectomy was advised but was refused. Rapid extension of the gangrenous process took place to the second toe and the adjoining sole of the foot. This toe was amputated and the wound debrided but gangrene promptly extended to beyond the middle of the sole. At this time the popliteal artery was no longer palpable. It was obvious that

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there was no hope for the leg but sympathectomy was again advised in the hope that it would make it possible to save the knee. Consent was given this time and on March 8th, 1947, the 2nd, 3rd and 4th right lumbar ganglia and intervening chain were resected. Within a few days the level of gangrene seemed to demarcate although the base of the wound remained dirty. Histidine and ascorbic acid were tried without effect. On April 10th mid-leg amputation was performed. At operation all major vessels were seen to be occluded but nevertheless the color of the muscle was good and fair bleeding was observed from the small vessels in its cut surface. The stump was closed primarily without drainage and primary healing was obtained.

The patient was discharged, ambulatory on crutches on May 21, 1947. In August, 1947, despite his age, he was fit with a prosthesis. With this and a cane he managed quite satisfactorily but unfortunately gangrene of the left foot developed in November. Studies before and after sympathetic block indicated that no improvement could be anticipated from sympathectomy. The gangrene advanced and mid-leg amputation was performed on November 19, 1947. Primary healing was not achieved. Healing by secondary intention progressed slowly until in April, 1948 only a superficial 1.0 cm. crusted area remained unhealed. Despite this he was fit with a second prosthesis and not only has he learned to walk with the two artificial limbs, but he has found part-time employment as a cashier. As of June, 1948, the right stump is soft, pliable and asymptomatic, while the unhealed area on the left is smaller and slowly completing its healing.

Case 4.—J. T., Sydenham Hospital No. 102001, was a 66-year-old male diabetic who had been in another hospital in February, 1947, in diabetic coma, and with a slight infection of the right great toe. He was discharged with the infection incompletely cleared and was admitted to Sydenham Hospital on March 14, 1947. His temperature was 105 degrees. The right great toe was gangrenous with marked local suppuration and cellulitis extending over about half the dorsum of the foot. There was marked peripheral arteriosclerosis. The right foot, despite the cellulitis, was colder than the left. No pulses were palpable in the right foot but the popliteal artery was palpable. Severe diabetic acidosis was present. Penicillin was given and the acidosis controlled by appropriate measures. Histamine flare and saline absorption tests showed extensive impairment of the collateral circulation. Lumbar sympathetic block was done with an excellent response, the foot becoming appreciably warmer.

Right lumbar sympathectomy was performed on March 21st, excising the chain from below the first lumbar to above the fourth lumbar ganglia. The foot after operation was definitely warmer. Following the procedure, the necrotic skin of the gangrenous toe was excised without anesthesia on the ward. About a half ounce of pus was evacuated. Necrotic extensor tendons were seen in the base of the cavity. On April 7th the great toe and the distal half of the first metatarsal were amputated and the soft tissue debrided. Healing was complete by the 9th of May on which day the patient was permitted to walk without crutches.

Case 5.—N. L. Beth David Hospital No. 47-2072, was a 59-year-old man admitted on May 16, 1947, with a history of progressive coldness and numbness of both feet and severe pain in the left foot and leg on walking. He had been given a course of histidine and ascorbic acid at another hospital not only with no relief but with progression of the pains to a degree where they were present even at rest.

There was marked peripheral arteriosclerosis. Roentgenogram of the leg showed calcification of the arteries. The feet were cold and moist with dependent rubor and ischemia in the elevated position. Neither dorsalis pedis nor posterior tibial was palpable. Both popliteal pulses were diminished. Oscillometry showed markedly reduced readings bilaterally. Orthopedically the feet were bad; there was bilateral halux valgus, marked pes planus, and the second toe overlapped the great toe of each foot. He stated, however,

that these findings had no relation to his complaints. Upon left lumbar sympathetic block increased warmth and complete amelioration of symptoms resulted.

On June 13, 1947, the left lumbar sympathetic chain was excised from below the first to above the fourth lumbar ganglia. Following this procedure pain disappeared entirely and definite warming of the member was achieved. He was discharged on June 26th walking well. There was insufficient subjective symptomatology referable to the right lower extremity for sympathectomy on this side at the time.

The patient has been seen on several occasions since the operation, the last on March 9, 1948. The increased warmth of the left leg and foot persists and he is now able to walk any distance required by his normal activity (up to ten blocks) without pain.

Case 6.—I. H., Mt. Sinai Hospital No. 575474 was a 55-year-old male private patient admitted on January 16, 1948, with a history of intermittent claudication in the left leg for five years. This had progressed to a degree where he was unable to walk more than a block before it set in. He had sold his car because cramps developed in the left calf after driving a short distance. On examination there was marked peripheral arteriosclerosis with absence of the posterior tibial, dorsalis pedis and popliteal pulses on the left. All were palpable but diminished on the right. Both feet were cold, with dependent rubor, more marked on the left. Oscillometric readings were practically absent from the left leg and markedly diminished on the right. Histamine flare and saline absorption tests showed marked impairment of the collateral circulation. Roentgenograms showed calcification of the vessels. The response to left posterior tibial nerve block was excellent with marked warming over the area of distribution of the nerve.

Left lumbar sympathectomy was performed on January 17, 1948, excising the chain below L-1 and above L-4. The result was phenomenal. Within ten days after operation the patient walked eleven blocks, at which time he developed claudication in the opposite calf and fatigue of both thighs. At his request right lumbar sympathectomy was performed on January 28th. The result was again excellent.

The patient was seen last on May 5th, 1948, at which time his legs and feet were warm and dry and he was able to walk almost limitlessly without claudication until fatigue or boredom caused him to stop. About 12 blocks was the distance of his usual walks and not infrequently this was extended to more than a mile.

DISCUSSION

In the above series, eight lumbar sympathectomies were performed upon six patients with advanced, symptomatic peripheral arteriosclerosis. Although the series is small, the variety of lesion included represents a cross section of those that may be encountered. In all cases, the degree of sclerotic vascular obliteration was severe, with both subjective and objective evidence of marked circulatory deficiency. In only one of the eight extremities were pulses in the foot even faintly palpable. Gangrene, with or without ulceration and infection was present in five instances. Despite the advanced degree of organic change and the complicating lesions, definite benefit was achieved in seven of the eight cases, and limbs were saved that would otherwise probably have been lost.

Incapacitating intermittent claudication was the indication for sympathectomy in two cases (Cases 5 and 6). In both, the feet were cold and moist, with dependent rubor and blanching on elevation. Their response to block was good. Both achieved remarkable relief from sympathectomy, unilateral in one, bilateral in the other. Case 5 now walks up to 10 blocks and severe rest pain and the sensation of coldness of the limb have also been relieved. In Case 6

the capacity to walk has been increased from about a city block to an indefinite distance. Sympathectomy was performed on the second side at the patient's request as after its performance on the side of which he originally complained, his ability to walk increased to such a degree that intermittent claudication developed on the previously better side.

Cases 1, 2, and 4 were admitted with gangrene of one or more toes and accompanying infection. In addition, Case 1 had a large dirty ulcer over the dorsum of the left foot with exposure of the extensor tendons in the base of the ulcer. In all of these, after sympathectomy, only toes were lost, with relatively asymptomatic use of the remainder of the member. This was of particular importance in Case 2 where one leg had already been amputated.

Only in Case 3 is it questionable whether anything was accomplished since at the time that sympathectomy was performed extensive spreading gangrene of the foot was present and it was already accepted that the limb could not be saved. The purpose of sympathectomy in this case was to lower the level of the necessary amputation from above the knee to the mid-leg. Incidentally, in this case, various medical methods of treatment had been unsuccessfully tried before sympathectomy was permitted. Despite the occlusion of all major vessels demonstrated at operation, primary healing was obtained, obviously the result of an increased collateral circulation. While hardly conclusive, it is possible that this primary healing at the mid-leg level was attributable to the preliminary sympathectomy, particularly since on the other side, later amputated without sympathectomy, primary healing was not obtained.

The question of the propriety of attributing the results that were obtained to sympathectomy may be raised. The experimental work of certain investigators indicates that the blood supply to the muscles of the leg is not directly controlled by the sympathetic nervous system (Grant, Friedlander, Silbert and Bierman) and on the basis of such data it has been stated that results achieved are independent of the operation. On the other hand experimental work by Grimson and Shen indicates that the blood vessels of skeletal muscles do react to vasomotor impulses by vasoconstriction and dilatation. This was demonstrated on both normal and skinned limbs, showing that the vasomotor phenomena occurred equally well in both. If this is the case, sympathectomy would result in the elimination of whatever vasoconstrictor phenomena were present and promote healing.

I do not feel, however, that it is essential to analyze the validity of experimental work on vasomotor influence upon blood flow to the extremities in an effort to predict what the effect will be in humans with vascular disease. This is particularly so since there is a fairly large body of clinical material which gives, to my mind, indisputable evidence that circulation has been improved by the procedure (*vide supra*). While a decided increase in basal blood flow may not be expected after sympathectomy, as de Takats points out, fluctuations in blood flow due to influences of cold, standing and emotion do occur even in limbs with marked obliterative sclerosis and these are unquestionably eliminated. He demonstrates by oscillometric graphs before sympa-

thectomy the existence of such vasoconstrictor phenomena, and the elimination of these after sympathectomy. Moreover, both clinical examination and the usual circulatory tests have demonstrated an improvement in the circulatory status after sympathectomy both in our series and in those of others, even to the appearance of pulses which were absent before operation. And why it should be accepted that vasoconstriction operates in thromboangiitis obliterans if the blood supply to the leg muscles is independent of the sympathetic system, yet not in arteriosclerosis, is difficult to understand.

The most striking evidence, however, is contained in the clinical results in the body of case material which has been accumulated. In his discussion of de Takats' article, Ochsner states that the functional result is more important than oscillographic recordings. It is indeed difficult to attribute the disappearance of intermittent claudication after sympathectomy to anything other than the operative procedure, presuming, of course, that there has been a follow up of sufficient length to show that the result obtained is not evanescent. Insofar as the ulcerative and gangrenous lesions in our series are concerned, while it is of course possible that these might have gone on to healing without sympathectomy, as a rule lesions such as those described almost invariably come to major amputation. This was avoided in all but one of our cases, a case in which sympathectomy was done not with any hope of saving the foot but merely to insure the success of amputation at the mid-leg level. These results, I must add, are no longer novel and are simply corroborative of a much larger volume of material already referred to.

The various non-surgical methods of treatment of circulatory deficiency in peripheral arteriosclerosis (diethyl-ether, histidine and ascorbic acid, tetraethyl ammonium bromide, alpha tocopherol, etc.) have not seemed to have any comparable benefit in our hands. The operation itself, utilizing the Pearl approach as described by de Takats, is an extremely bland one with little or no mortality. It rarely takes more than a half hour to 45 minutes even in obese individuals and disturbs the patient less than a simple appendectomy. Naturally, preliminary testing by sympathetic or peripheral nerve block serves as the basis for selection of cases for the operation. Alcohol sympathetic block is not to be recommended as its effect is frequently incomplete and impermanent, and serious complications are not uncommon.

In conclusion I should simply like to reiterate the purpose of this report which is again to call attention to the fact that a simple operative procedure offers hope for staying the course of an otherwise dread progressively incapacitating malady. The reported results have been good out of proportion to the degree to which the profession at large has indicated their willingness to make use of the procedure. It is in the hope that a more widespread utilization of lumbar sympathectomy in the treatment of selected cases of peripheral arteriosclerosis will result, that this report is made.

SUMMARY

1. The literature on the use of lumbar sympathectomy in the treatment of obliterative vascular sclerosis is reviewed.

SYMPATHECTOMY IN ARTERIOSCLEROSIS

2. A series of eight extremities with advanced, symptomatic, complicated lesions treated by lumbar sympathectomy is presented.

3. The rationale and efficacy of the procedure are discussed, and an appeal for its trial in selected cases made.

ADDENDUM: Since this article was submitted for publication two cases with sufficient follow-up are to be added to the series. One was a private patient of Dr. Morris Steinberg, a 54-year-old male diabetic and arteriosclerotic, who developed an area of gangrene on the heel of a cold, pulseless extremity. The gangrenous area healed completely following lumbar sympathectomy. The second was a private patient of Dr. Henry Dolger. This was a 65-year-old woman with diabetes and arteriosclerosis who had been completely incapacitated by a popliteal artery embolus six months previously. The limb was pulseless and cold and there was pain even at rest. Following left lumbar sympathectomy, the color and temperature improved, the pain disappeared, and the patient is now able to walk five blocks without appreciable effort or distress.

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TISSUE REACTION TO PLASTICS USED IN SURGERY WITH SPECIAL REFERENCE TO TEFLON*†

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SURGEONS' INTERESTS in plastics have been confined in the past to its application as suture material. The increasing use of internal prosthetic devices has made surgeons more aware of the adaptability of plastics to these problems.

Plastics have been used to fill in bony defects in reconstructive and maxillo-facial surgery, to replace missing segments of calvarium in neurosurgery, in replacing large defects of the thoracic cage, as a non-suture device in blood vessel anastomosis, to replace large segments of vessels experimentally, as blood vessel catheters, and in a host of other applications. Since the majority of the plastics that have been investigated are non-absorbable, the limiting factor to their use would be the production of tissue reaction.

The factors which cause tissue reaction in non-absorbable plastics can be attributed to their chemical and physical properties. Chemical inertness and insolubility have given the impression that many plastics would be free of tissue reaction. This supposed chemical inertness may, however, be misleading, since glass also is apparently inert yet able to produce marked reaction. Another factor to be considered is the addition of so called plasticisers in the process of manufacture. These chemicals and other chemicals added for coloring purposes have a tendency to "sweat out" of the plastic and may produce intense tissue reaction.¹ To further confuse, there are many different chemical formulas for commercial plastics marked under names such as lucite, plexiglass, etc. Some forms have added plasticisers, others have not.

Too little attention has been paid to physical characteristics of foreign substances which may incite tissue changes. In the case of metals, the galvanic effect is capable of producing tissue necrosis.² The surface charge of foreign materials should be equally important. In addition, interfacial tension and ability to be wet by water should also be factors of considerable consequence. Gortner and Briggs,³ utilizing the method of streaming potentials, showed that there was a high electronegative charge on the surface of glass in contact with water. When the glass was coated with paraffin, which cannot be wet by water, the surface charge was zero. They postulate that absorption of positively charged colloids from serum might explain decreased clotting time in glass

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vessels as compared to paraffin coated vessels. Similar effects may take place with instillation of supposedly inert foreign material into living tissue. Carbon particles, although chemically inert, are capable of producing fibrosis when inhaled by humans or injected into the peritoneal cavity of animals.⁴ Since the carbon is chemically inactive, the fibrosis must depend upon physical factors. Such factors have received little attention in the past.

In previously described methods of study, the substance to be tested has been embedded in the tissues with subsequent observation of tissue reaction.^{5, 6, 7, 8, 9} Such methods will reveal but minimal tissue reaction since only a small surface area of the substance is exposed to the tissue. We were impressed by the methods used in testing the foreign body reaction of dusts by the United States Bureau of Mines.⁴ In this method the dust, which is finely divided, and has a relatively large surface area per unit mass, is injected into the peritoneal cavity which offers a large surface area of tissue for reaction to occur. By examining the peritoneal cavity at a later date it has been possible to predict whether an inhaled dust would produce pneumoconiosis, silicosis, or no reaction. We, therefore, studied the peritoneal reaction to finely divided plastic in order to evaluate its tissue reactant capacity.

We have also studied the tissue reactions to a new plastic "Teflon,"* which is one of the most chemically inert plastics yet discovered and which has unique physical properties. The plastic is semiflexible, having bending properties somewhat analogous to lead, but it is more brittle. This plastic can easily be cut and shaped with a knife. It has a distinct waxy feel. The most unusual property of "Teflon" is that it cannot be wet with water. Nothing will adhere to it and, once formed, it cannot be cemented to any other known substance. The singular physical properties of this chemically inert plastic prompted us to study its tissue reaction along with other plastics.

MATERIALS AND METHODS

Implantations of the plastic materials were made in 21 dogs. The materials were implanted in various sites for purposes of comparison. The extent of division of the material was varied to show the effect of increasing the exposed surface area. The dogs were sacrificed at periods varying from 36 hours to six months postoperatively, at which times specimens were obtained for microscopic study. Routine aseptic surgical technic was altered only in that no gloves were used to avoid possible tissue reaction caused by the various dusting powders. The hands were carefully scrubbed and immersed in alcohol. All of the animals were given 300,000 units of penicillin in oil and beeswax postoperatively to minimize the possibility of infection and its resultant tissue responses. All plastics were placed distant to sutures. Cotton thread was used as the suture material throughout.

The materials studied in this way were FM-1 nylon, celluloid, lucite, and teflon. All materials used were free of plasticisers and color. The materials

* Furnished through the courtesy of E. I. Dupont & Co., Arlington, N. J.

were carefully washed and cleansed and copiously rinsed with distilled water. Sterilization was accomplished in an autoclave.

In an additional experiment, a suspension of extremely small particles of cellophane was made according to a method described by Cannon & Marshall for collodion.¹⁰ These washed and suspended particles pass easily through a fine gauge needle. This material was injected into the peritoneal cavity of four guinea pigs.

Although a similar type of suspension can be made with lucite, we have been unable to prepare satisfactory suspensions of nylon, polythene or teflon by chemical methods. Mechanical methods utilizing filings also fail to produce sufficiently small particles for suspensions which could be injected through a fine needle. It is possible that suspensions could be made of these materials in a colloid ball mill although we have not investigated this possibility. Lucite, celluloid and nylon were obtained in a finely divided state by taking the shavings produced by drilling holes in the solid material. Teflon was finely divided by taking small slices from a rod in fashion similar to that used for cutting paraffin sections on a microtome.

Microscopic sections were made in all cases at the time the animals were sacrificed for gross observations.

RESULTS

Celluloid—At the end of three days, an intense fibrinoplastic reaction was seen. The peritoneum was lusterless and granular. The omentum, bowel and adjacent tissues were edematous, hyperemic, and matted. The fat was indurated and friable and generally contracted. The peritoneal cavity contained small quantities of serosanguineous exudate.

The omentum was no longer discernible as a distinct structure. Microscopic sections confirmed the presence of acute inflammatory changes with infiltration of polymorphonuclear leucocytes. There was extensive edema of protein rich fluid. Protein material adsorbed on the surface of the plastic was discernible as a distinct layer. The capillaries were engorged and showed diapedesis of cells in some areas. The reaction was most intense with celluloid as compared to the other plastics.

In 70 days, the acute inflammatory reaction had subsided. Loops of bowel were bound to one another and to the omentum by dense fibrous tissue. The shrunken fibrous tissue had pulled bowel and omentum into a solid mass.

Microscopic sections taken at the 70-day interval show active fibroplasia, extending some distance from the site of plastic implantation. Epithelioid fibroblasts and giant cells were present in areas adjacent to the plastic. In some areas, chronic inflammatory changes could be seen with infiltration by some polymorphonuclear leucocytes, plasma cells, large and small lymphocytes, macrophages, and Langhans' giant cells. In the fissures of the solid plastic, pigment similar to hemosiderin was visible. Again the plastic material was always coated by a thin layer of protein.

Lucite—After three days, the reaction to lucite was similar to that observed with celluloid but not quite as intense.

Acute inflammatory changes were present which caused an extensive matting of all tissues exposed to the lucite. None of the plastic material could be found free in the peritoneal cavity. In one dog, a dilated loop of small bowel was seen entering a matted mass (Fig. 1). Microscopic sections showed extensive acute inflammatory changes.



FIG. 1.—Photograph of the peritoneal cavity of a dog 3 days after implanting fine lucite shavings—Omentum and bowel form a large inflammatory mass. A loop of partially obstructed and dilated small bowel, to which an Allis clamp is attached, is visible at the lower angle of the abdominal incision. At the upper angle, a Kocher clamp retracts the abdominal wall to show dense adhesions between it and the liver. An additional Kocher clamp immediately below grasps a dense adhesion which was severed. None of the leucite shavings lie free in the peritoneal cavity, all are covered by reddened inflammatory tissue.

Dogs sacrificed after the 70-day interval, showed the same dense fibrotic changes which occurred with celluloid implantation after a similar period. No marked quantitative differences could be seen either grossly or microscopically.

when compared to the late celluloid changes described above (Fig. 2). It was apparent that the process had not yet become inactive.

Nylon—We were somewhat amazed to find that the peritoneal reaction to finely divided nylon was identical with that described for lucite (Fig. 3).

Teflon—On comparing the reactions of the above plastics to teflon very striking differences were seen. Finely divided chips of teflon were seen to be

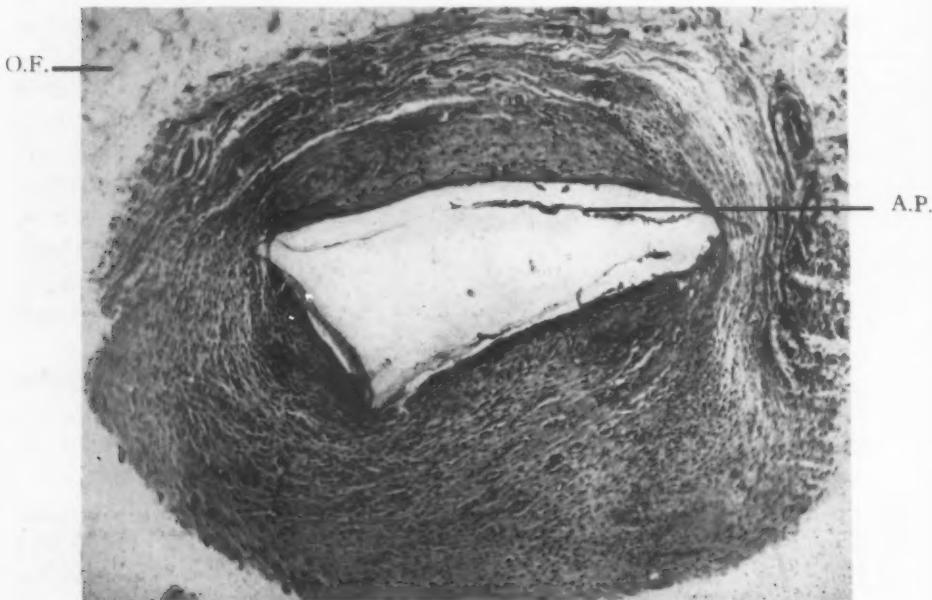


FIG. 2.—Lucite shaving in peritoneal cavity. The fibrosis can be seen to extend some distance from the plastic completely replacing omental fat. A thin layer of adsorbed protein (A.P.) is visible on the surface of the plastic.

The large dark spots in some areas represent foreign body giant cells. Uninvolved omental fat (O.F.) is present on one corner.

lying free in the peritoneal cavity. There were no acute inflammatory changes and no gross evidence of tissue reaction (Fig. 4). Occasionally chips could be seen encased in omentum, but the extent of peritoneal reaction was certainly no more than would be expected from simple surgical manipulation.

At the end of 70 days most of the chips were surrounded by omentum. There was no fibroblastic reaction and the chips could be easily removed from the flimsy omental adhesions which were broken with ease.

The reaction to implanted teflon is illustrated in Figs. 5, 6 and 7.

A thin fibrous sheath of mature fibroblasts surrounded the plastic by the end of 70 days. No proliferative foreign body reaction was present.

By the end of six months, the delicate fibrous capsule surrounding the plastic had not increased in thickness (Fig. 6). An intact mesothelial-like layer on the omentum exposed to the plastic (Fig. 7), emphasized the plastic's inability to produce tissue changes, and suggested that the fibrous capsule was

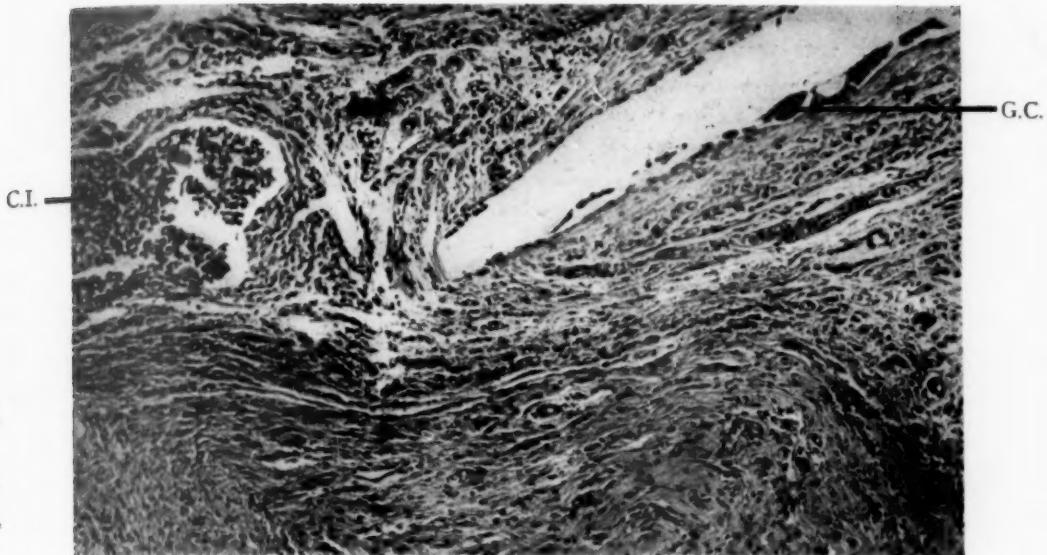


FIG. 3.—Photomicrograph omental tissue adjacent to Nylon for 70 days.

The active fibroplasia is evident. The fat tissue has been completely replaced with fibrous tissue of varying age. At one edge is seen an area of chronic inflammation (C.I.). Foreign body giant cells (G.C.) are also seen in the tissue which was adjacent to the plastic.

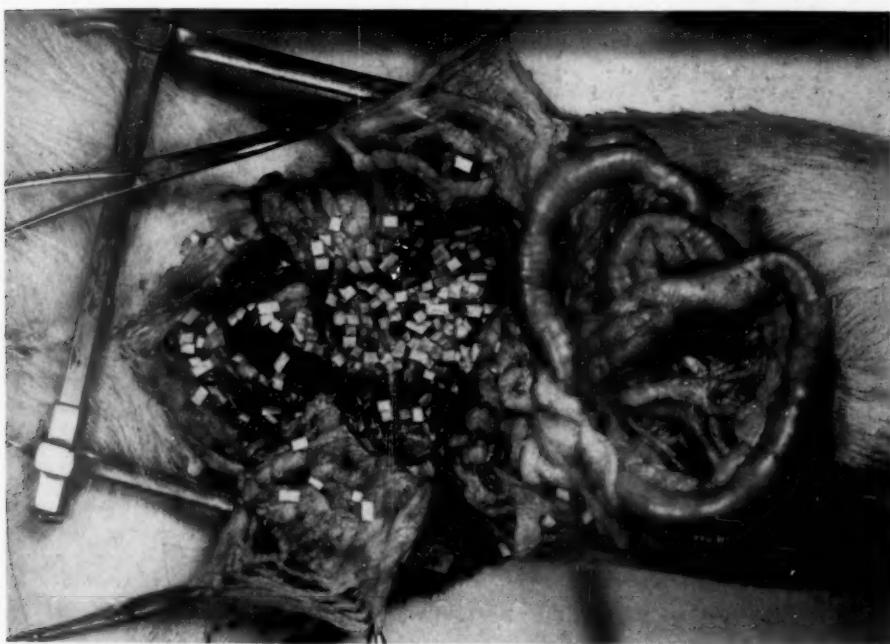


FIG. 4.—Photograph of the peritoneal cavity of a dog 3 days after the instillation of fine microtome slices of teflon. There is no matting of bowel or omentum and the chips are seen to lie free in the peritoneal cavity. The stretched out omentum shows its thinness and the absence of even a vascular response.

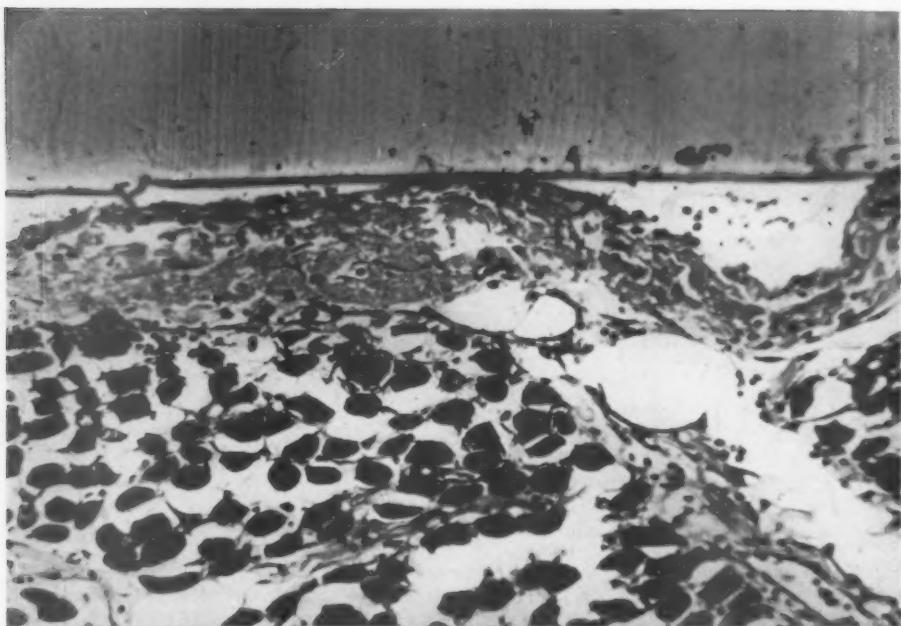


FIG. 5.—Photomicrograph of teflon implanted in muscle tissue 3 days after implantation—There is a somewhat cellular debris immediately adjacent to the teflon caused by surgical trauma. Observe the absence of early polymorphonuclear leukocytic response.

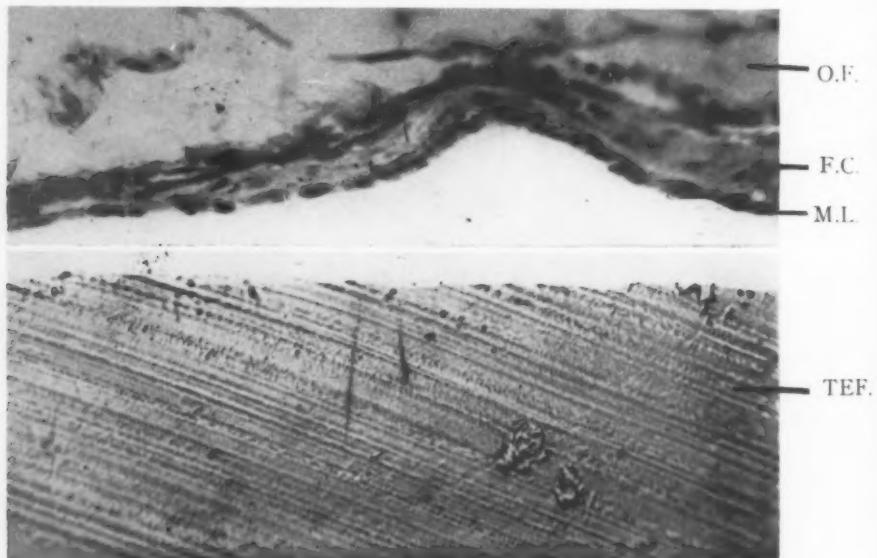


FIG. 6.—Photomicrograph of teflon strip in peritoneal cavity at 6 month interval.

Notice the thin layer of mature fibroblasts (F.C.) under the intact mesothelial layer (M.L.). No fibrosis is seen extending into omental fat (O.F.). The adjacent plastic (TEF.) shows no adsorption of protein.

caused by trauma rather than by tissue reaction. In contradistinction to all the other plastics, the surface of teflon in all sections was free of adsorbed protein.

With the exception of teflon, the various plastics produced more intense reaction when finely divided material was placed in the peritoneal cavity than when tissue implantations of large pieces of material were performed. In addition, plastic implantations into tissues necessitated varying amounts of surgical trauma which was difficult to evaluate when estimating the degree of tissue response incited by the foreign material alone.

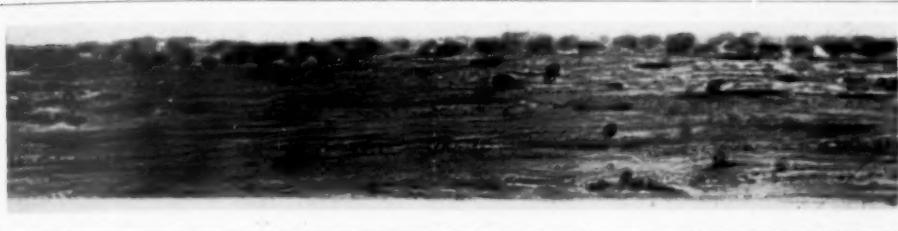


FIG. 7.—High power photomicrograph of omentum adjacent to plastic. Notice the intact mesothelial lining and the very thin layer of mature fibrous tissue immediately beneath it.

Cellophane—The four guinea pigs in which the suspension of cellophane was injected intraperitoneally were sacrificed 7 days, 12 days, 21 days, and 2 months following injection. A late fibrotic response comparable to that described by others was observed.^{11, 12}

DISCUSSION

Nylon and lucite plastics, which have been reported as free of tissue response,^{6, 7, 13, 14, 15} are really potent excitors of tissue reaction. Previous observations are explained when one considers that but a small surface area of the plastic had been exposed to an equally small surface area of tissue. The changes therefore take place in miniature. The end result is a dense fibrous capsule surrounding the plastic. This type of reaction is seen with many non-absorbable materials.

Whether the tissue reaction is due to the dissolution of traces of the unpolymerized chemicals used in plastic manufacture or actually to the solution of an infinitesimal amount of the plastic itself cannot be determined. The authors believe that the physico-chemical characteristics of the surface of the foreign material has much to do with tissue reaction. If proteins or water are adsorbed on the surface of the plastic, the molecular configuration must necessarily be altered from that of adjacent tissue. With regard to this hypothesis, microscopic studies on all the plastics, with the exception of teflon, showed adsorption of protein on the plastic surface. All but teflon produced a proliferative foreign body reaction. Knisely has demonstrated that India ink particles injected into the blood stream are coated with a protein material before phagocytosis can occur. The adsorption of protein by plastic surfaces, which can be wetted may similarly affect the production of giant cells and proliferative foreign body reaction. Physico-chemical factors are potent stimuli in wound healing. When

the orientation of each molecule to its adjacent molecule has been restored, the proliferative reaction associated with wound healing ceases. Since metallic surfaces can also be wet with water, it would be important to restudy these substances by the intraperitoneal method.

In testing for tissue reaction to foreign material, it is essential that the greatest possible surface area of the material be exposed to the greatest possible surface area of tissue. This is best accomplished by injecting the powdered material suspended in saline into the peritoneal cavity of the experimental animal. Such a test is the most delicate indicator of tissue response. The animals should be sacrificed at the end of three days and three months to ascertain the effects. Gross observation seems sufficient. Plastics which produce tissue response when tested by this method may still be useful in surgery. However, the surface should be well polished to reduce surface area. It is certainly wiser to substitute a material which does not have these disadvantages.

Because nothing will stick to teflon, it suggests itself as an ideal substance for bile duct tubes,* where formation of concretions has been a problem. Polythene, which also is somewhat water repellent, more recently has been so used.¹⁶ It should be pointed out, however, that a wide discrepancy exists in the published reports on the tissue reaction to polythene. Ingraham⁸ found polythene to be virtually a non reactor, while Poppe²⁰ states that polythene film induced even a greater fibroblastic response than cellophane. It was the most sclerotic substance tested. (Dupont & Co. was the source of the material in each case.) This tissue reaction may result from dicetyl phosphate incorporated in the polythene during certain methods of manufacture.²³

Teflon should be suitable for intravenous catheters and for replacing segments of small blood vessels, since blood does not clot on materials which cannot be wet with water.¹⁷

Page and others^{11, 12} have shown that cellophane produces a marked fibroblastic response in the tissues. Cellophane can be wrapped around large vessels¹⁸ to produce gradual occlusion or to fibrose aneurysms.^{19, 20, 21} As a corollary, our work suggests that colloidal suspensions or even coarser suspensions may be injected through small needles to produce the same sclerosing effect. It, therefore, seems possible to occlude such major vessels as the abdominal aorta by injections into the surrounding adventitial tissue without the necessity of operation. Since powdered cellophane would expose the greatest possible surface to the tissue, this method seems the most logical. Caution should, however, be exercised in the clinical use of cellophane since sarcomas have been induced in a high percentage of laboratory animals by cellophane implantation.²²

It is suggested that there be a standardized method for testing tissue reaction to foreign substances. This method should have maximum sensitivity so that minor differences may be appreciated. Such a method would have the ad-

* The Zack Manufacturing Co., 1422 So. Cuyler, Berwyn, Ill., supplies many of these various appliances.

vantage of providing a base line for comparison and be sufficiently objective to offset the personal equation in interpretation.

The injection of finely suspended material would be ideal. Some such suspensions can be manufactured chemically; others may be formed by the use of a colloid ball mill. If fine suspensions cannot be made, the intraperitoneal instillation of finely divided material will give adequate information.

SUMMARY AND CONCLUSIONS

The surface area of both the foreign substance and the tissue exposed are important factors in determining tissue reaction. Intraperitoneal instillation of finely divided foreign materials is therefore the testing method of choice.

Chemically inert plastics which cannot be wet with water produce the least tissue response. The tissue response to a number of plastics including a new plastic, teflon, has been described. Some practical applications evolving from these studies have been suggested.

Appreciation is expressed to Dr. Eleanor Humphreys, whose many suggestions and pathologic opinions made this work possible.

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EXPERIMENTAL PULMONARY COLLAPSE*

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THE ABILITY OF CERTAIN SYNTHETIC PLASTIC MATERIALS to incite fibrosis has been described by several investigators. Page¹ used cellophane to produce fibrosis of the kidney capsule. Pearse² studied the effect of the same material on blood vessels. Poppe and de Oliveira³ found that polyethylene produced fibrosis of the aorta in dogs. Ingraham, Alexander, and Matson,⁴ reviewing the use of these materials in surgery, conclude that cellophane is irritating to tissues and that the effect of polyethylene is variable owing to differences in its manufacture for commercial purposes; pure polyethylene tubing is non-irritating. These studies suggested that it might be worthwhile to investigate the fibroplastic effect of cellophane and polyethylene on the pleura and lung to determine if pulmonary fibrosis or collapse could be produced.

Experiments were carried out on healthy mongrel adult male dogs weighing 3.9 to 12.7 kg. Nembutal and ether were employed for anesthesia. With aseptic technic pleurotomy was performed and a sheet of plastic material was wrapped about the dorsal, ventral and lateral surfaces of one lung, which was re-expanded at time of closure of the wound. A total of 12 animals was used. These were sacrificed three to six months after operation. Autopsies were performed, findings were photographed, and sections made of tissues from treated and untreated sides.

The plastic materials used were cellophane and polyethylene which were obtained in the form of sheets.* Before use, the material was sterilized by immersion in 1:1,000 aqueous zephirin solution for one hour, after which it was washed in sterile physiologic saline solution.

CHANGES PRODUCED BY CELLOPHANE

The changes produced by cellophane were somewhat fulminating in the two animals in which it was used. There was exudation of serous fluid requiring thoracentesis—once in one animal and on numerous occasions in the other animal. Both recovered, however, and were sacrificed three months after operation. At autopsy, the chest wall and entire lung were collapsed toward the mid-line; the heart and mediastinum were not displaced. The greatest diameter of the unoperated thoracic cavity was 6 cm., that of the operated side was 1 cm. The operated thoracic cavity contained a tough fibrous mass of thickened pleura, collapsed lung, and cellophane. The cellophane retained its characteristic structure and strength; it had not been

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** Cellophane, 300 PUT-71; Polyethylene, 1.5 mil polythene, sample No. 4553. These were kindly furnished by Mr. A. S. Taylor, Cellophane Division, E. I. DuPont de Nemours and Company.

invaded by tissue. The lung of the untreated side and the heart and pericardium were normal. Sections revealed extensive fibrosis of the pleura, both parietal and visceral. The lung showed absence of air spaces, increased cellularity due to connective tissue cells, and some increased interstitial collagen formation. Because of intense early irritative reaction in response to cellophane, the remainder of the experiment was carried out with polyethylene film.

CHANGES PRODUCED BY POLYETHYLENE

This material was placed over the lung on one side in ten different animals. The early severe irritative reaction noted with cellophane was not encountered with polyethylene—the operation was tolerated well. No animals required thoracentesis; all maintained weight, were active, and appeared healthy. One animal developed a sinus from the lower end of the operative wound five months after operation (see page 87). The animals were sacrificed at intervals after operation, one group after three months and one group after six months.

Changes produced after three months. Four animals were examined for changes in the thorax three months after application of polyethylene over the lung. In one, no changes were produced; neither the lung nor thoracic cage were collapsed. The sheet of polyethylene film remained unchanged in the pleural cavity. The pleura was normal except at the region of the operative scar. In the other three animals of this group moderate degrees of collapse were produced. The thoracic wall on the treated side was pulled medially because of a capsule of thickened visceral and parietal pleura which enveloped the plastic film. The mediastinum was shifted slightly to the affected side in one animal.

Sections of treated lung from this group showed patchy increase of interstitial collagen with collapse of air spaces. Intervening spaces of lung presented a normal appearance. The pleurae were greatly thickened due to fibrosis. The plastic material had not been invaded by fibroblasts. It appeared that extensive collapse was not achieved in three months.

Changes produced after six months. The treated side of the thoracic cages of the six animals sacrificed after six months showed marked degree of collapse of the chest wall and lung (Fig. 1) comparable to that noted in the animals treated with cellophane. The plastic sheet was found to be wrinkled and in some instances bunched and to be encased in a thick fibrous envelope which had been thrown out by the parietal and visceral pleurae. The action of this fibrous envelope apparently resulted in collapse of the chest wall medially and, in turn, collapse of the lung. The mediastinum was shifted little if any to the operated side; the pericardium was in no way affected since the plastic sheet had not been placed in direct contact with it. The lung on the unoperated side was normal both grossly and histologically (Fig. 2).

Sections of collapsed lung in these animals showed uniform increase in the density of the lung tissue. The air spaces were obliterated or greatly reduced by collapse and by interstitial fibrosis. New collagen was abundant

EXPERIMENTAL PULMONARY COLLAPSE

about the capillaries and in the alveolar walls (Fig. 3). The pleura was greatly thickened.

In one animal of this group, a sinus opened spontaneously in the operative wound during the fifth month. Serous drainage from this sinus was apparently due to foreign body reaction since cultures of the fluid during life and at autopsy exhibited no growth. The sinus, explored at autopsy, extended into



FIG. 1.—Collapse of the right side of the thorax and of the lung six months after application of polyethylene film about the lung. The anterior part of the thickened pleura and plastic material have been removed. Note loss of normal flaring curve (present on the left) on the right indicating collapse of the chest wall.

an interspace and directly to a small pocket bound by thickened pleura on one side and polyethylene film on the other. No free fluid was found elsewhere. The usual degree of collapse of the chest wall and lung was produced.

In another animal an attempt was made to collapse a portion of lung by confining the application of cellophane to the upper lobe only. This was successful in collapsing the lobe and adjacent chest wall. The remainder of the pleural cavity remained free of adhesions.

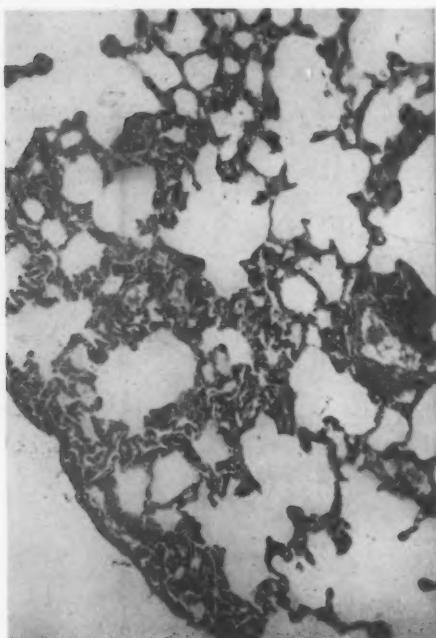


FIG. 2

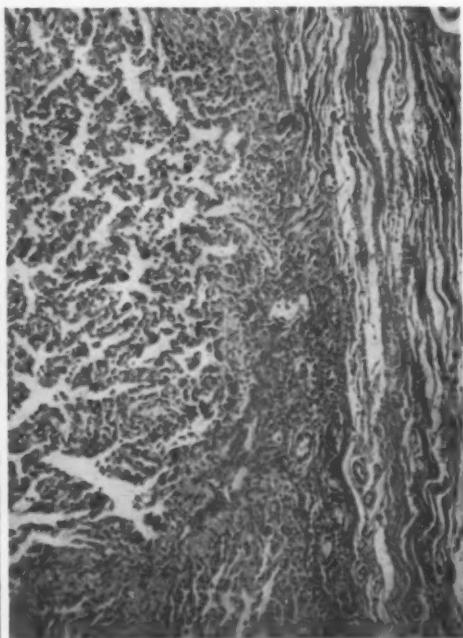


FIG. 3

FIG. 2.—Section of lung from an untreated side. Van Gieson stain.
FIG. 3.—Collapsed lung and thickened pleura produced by polyethylene film placed over the lung. This section is taken from the junction of the lung (left four-fifths of the figure) with the visceral pleura (right fifth of the figure). Van Gieson stain.

DISCUSSION

It appears that cellophane or polyethylene film when placed over the lung in dogs will produce thickening of the pleurae and collapse of the chest wall and lung; some fibrosis of the lung follows. Polyethylene of the type studied seems to be as effective as cellophane and is free from fulminating pleural reaction produced by the latter substance. In one instance a late reaction to the plastic material resulted in an open sinus through the operative scar, but without detectable infection. The changes produced are compatible with life and health in dogs. Although comparative measurements of respiratory function were not made, it was observed that operated animals were as active as normal and exhibited no evidence of dyspnea.

One difficulty in further application of "cellophane fibrosis" to produce

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pulmonary collapse arises from the variability of plastic films with respect to ability to induce fibrosis. The fibrous reaction is apparently produced by plasticizers used in manufacture of the product for commercial purposes. The film, for medical purposes at least, is a convenient vehicle for maintenance of an irritating chemical in a certain location. More recently, Blakemore⁵ has indicated that polyethylene film of known fibroplastic qualities can be obtained.

Whether or not cellophane collapse of the lung would be applicable to collapse therapy of human tuberculosis is conjectural. The reaction of the pleura of a tuberculous lung might well be quite different from the reaction of healthy dog pleura. On the other hand it is quite likely that if the production of localized thickened pleura and adhesions should be desirable, as in obliteration of an emphysematous bleb, either cellophane or polyethylene of suitable composition would be quite effective.

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STREPTOMYCIN IN SURGICAL INFECTIONS. VII.
NONPULMONARY TUBERCULOSIS
(LYMPH NODES, URINARY TRACT, BONE, AND PERITONEUM)*

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THIS COMMUNICATION reports United States Army Hospital experiences with streptomycin therapy in 35 cases of tuberculous lymphadenitis, 46 cases of infection of the genito-urinary tract, 24 cases of tuberculosis of bone and 16 cases of ulcerative tuberculous enteritis.

TUBERCULOUS LYMPHADENITIS

Up to June 1, 1948, 35 cases of tuberculosis originating in the lymph nodes had been treated with streptomycin and fully studied in U. S. Army hospitals as part of the Army streptomycin program.

Previous Government Experience. In Government hospitals, 36 patients with lymphadenitis of proved tuberculous origin were treated with streptomycin prior to March, 1948. In 12 patients glands disappeared; in 18 they became smaller and in six they were unchanged in size. In addition to these cases, 51 patients with draining lymph nodes were treated and studied. Forty-five of the 51 were regarded improved, but the Committee could not state whether the lesions in these 45 disappeared or merely became smaller. The Committee regards streptomycin as of value in tuberculous lymphadenitis.

Army Experience. The age range in the 35 patients with tuberculous lymphadenitis in the Army series was from 18 to 52 years. The majority were in their early twenties. Fourteen patients had tuberculosis in other areas of the body, chiefly the lungs. In two cases the disease had spread to other parts of the body in addition to the lungs and the lymph nodes. In 26 cases the lymphadenitis was located in the anterior and posterior cervical chain. In four cases the axillary nodes were involved and in five the mediastinal nodes. In 16 cases the lesions had progressed to necrosis with sinus-formation and were discharging pus. In the remaining 19 cases the lymph nodes were enlarged but still intact. Diagnosis was by biopsy, supplemented in a few cases by cultures or by guinea pig inoculations.

The dosage schedule in most cases was 1.5 to 2.0 Gm. of streptomycin daily by the intramuscular route, given in three or five injections; in a few instances the dose was 1 Gm. a day given in two injections. The duration of

* Submitted May 10, 1948.

treatment ranged from 10 to 120 days; most of the patients were treated for periods of 10 weeks. Adjuvant local measures were employed in four cases.

Streptomycin therapy was used with two objectives in this series of cases. The first objective, in 26 cases, was to arrest the infection by the administration of the drug. In the other nine cases streptomycin was used before operation, to prepare the patient for surgery and to protect him against dissemination of the disease, and after operation, to lessen the danger of sinus-formation and metastases. In this group of cases the average period of administration was 56 days. Six of the 19 patients with simple lymphadenitis were treated by surgical measures, which were also employed in three of the 16 cases in which sinus-formation had occurred.

Uncomplicated Tuberculous Lymphadenitis. Thirteen cases of lymphadenitis without sinus-formation were treated only by streptomycin, with good results in nine cases and failure in four. One of the patients who had no results from streptomycin also had syphilis, for which he had been treated with penicillin for three weeks; the associated syphilitic infection perhaps played a part in the failure of the lymph nodes to regress. The other patient who had no results from streptomycin therapy had had scrofula for 18 years, and the disease was probably so far advanced that extensive fibrotic changes had resulted. Whatever the reason, there was no demonstrable change in the state of the lymph nodes at the end of 60 days of streptomycin therapy. The third failure was in a patient with widely disseminated miliary tuberculosis; and the last failure was in a patient with cervical lymphadenitis and minimal pulmonary tuberculosis in whom there was no regression after two months' treatment.

Six patients with uncomplicated lymphadenitis were treated with streptomycin in combination with surgical measures. In four cases the drug was used for 12 days, after surgical excision of tuberculous cervical lymph nodes, as a prophylactic measure to ensure primary wound healing. In the other two cases the patients were submitted to exploratory thoracotomy and biopsy of the mediastinal lymph nodes, and received streptomycin for 30 days, to protect against spread of the disease, poor wound healing and other complications. There was uncomplicated healing without spread of the disease in five patients and no change in one patient.

Tuberculous Lymphadenitis with Sinus Formation. There were 16 patients in this group, three treated with surgery and 13 without surgery. One of the three patients treated by surgical measures in this group had an "orange size" tuberculous abscess of the axilla; acid fast bacilli were recovered from the exudate. Streptomycin was given by the intramuscular route for 18 days before and 81 days after surgical drainage of the abscess, and the wound was dressed every other day with gauze impregnated with 1 Gm. of streptomycin dissolved in saline. The amount of exudate slowly decreased and the wound appeared well healed six weeks postoperatively. There has been no sign of recurrence in a six months' follow-up. The second patient treated by surgery was submitted to six weeks of streptomycin therapy for draining sinuses in the

neck originating in caseating, matted anterior cervical lymph nodes. The adenitis did not resolve. Drainage lessened but continued. Excision of the involved glands *en bloc* with the sinus tracts and surrounding skin was then performed. The wound healed solidly. Streptomycin was continued for three weeks postoperatively. There has been no recurrence in a four-months follow-up period. The third patient had a draining axillary sinus following incision three years previously. The tract and compromised tissue were excised and 1 Gm. of streptomycin instilled. The antibiotic was administered intramuscularly for 14 days postoperatively. The wound healed and has remained so.

In 11 of the 13 patients with tuberculous lymphadenitis complicated by sinus formation who were treated by streptomycin without surgery, the results were good. The sinuses healed during the course of therapy and there was impressive regression in the size of the lymph nodes, which in some instances disappeared so completely that they were no longer palpable. The remaining two cases in this group were therapeutic failures. The first patient who had no results from streptomycin therapy had miliary tuberculosis with draining cervical lymphadenitis. Death occurred after 115 days of therapy. Culture sensitivity tests shortly before death revealed extreme resistance to streptomycin of the organisms. In the second unsuccessful case streptomycin was given for 10 days, during which period the draining tuberculous sinuses closed. Streptomycin was not continued, however, because of the appearance of generalized purpura. It was realized that this development might be the result of a long previous course of salicylate therapy, but the possible responsibility of streptomycin could not be discounted. Three weeks after the interruption of therapy the sinuses re-formed and the amount and character of the drainage became essentially the same as before streptomycin had been given.

Comment. The follow-ups in the Army series of cases of streptomycin-treated tuberculous lymphadenitis are too short to permit generalizations as to the value of this antibiotic in this condition. Tuberculous lymphadenitis, however, is a notoriously obstinate condition, and the excellent results obtained in many cases (20 of the unoperated cases, and six of the operated cases in the series) suggests the propriety of the continued use of streptomycin in its management. Noteworthy is the fact that one failure could be attributed to streptomycin fastness of the organism and the other to streptomycin toxicity.

The results of streptomycin therapy were generally better and prompter when surgical measures were combined with it. Apparently the preoperative and postoperative use of this agent is helpful in preventing sinus-formation and in expediting the closure of sinuses which exist. The ideal treatment would seem to be saturation of the tissues by the administration of streptomycin at therapeutic levels for a period of one to two months. If at the end of that time there is no clinical response, and if the case is amenable to surgery, block dissection of the lymph nodes or removal of the primary focus of infection should be considered. Following surgery, the same therapeutic levels should be maintained until it is clear that primary healing has been accomplished. Packing the operative site with gauze saturated with a solution of streptomycin

was carried out in only three cases in this series, but would seem desirable as a means of shortening the period of disability. Moreover, cases which had been refractory to streptomycin before removal of the infected tissues might show improvement under this treatment after the local blood supply had become adequate.

Good results cannot be expected in tuberculous lymphadenitis unless the course of streptomycin therapy is adequate. Long courses of therapy may, however, give rise to toxic reactions and the patient should be carefully watched. (The use of dihydrostreptomycin may reduce the severity and incidence of neurotoxicity).

It was of interest in the Army series, when the same patient presented multiple involvement, that there was no apparent correlation between improvement in the local lymphadenitis and changes in pulmonary tuberculosis processes. Even in cases in which tuberculous lymphadenitis was apparently cured, roentgenograms evidenced no perceptible changes in the pulmonary disease.

TUBERCULOSIS OF THE GENITO-URINARY TRACT

Up to June 1, 1948, 46 fully studied cases of tuberculosis of various portions of the genito-urinary tract had been treated with streptomycin in U. S. Army hospitals as part of the Army streptomycin program.

Previous Government Experience. Up to May 1, 1947, streptomycin had been administered in 41 cases of proven genito-urinary tuberculosis in hospitals of the Army, Navy, and Veterans Administration. Thirteen of this group had 120 days of treatment and had multiple lesions of the genito-urinary tract, on an average of 3.5 lesions per patient. Cultures of vesical urine were made every fortnight and cultures of ureteral urine every 40 days during therapy. Nine of the 13 patients improved, but, in most cases, only temporarily as to frequency and dysuria. Vesical capacity increased in 10 of the 13. Cystitis diminished in 11 cases. Twenty-five of 32 lesions in the posterior urethra, prostate, and seminal vesicles improved. Only four of the 13 patients continued to have positive urine cultures after the first 40 days of treatment, and only two of these were positive one month after the conclusion of treatment. In both instances the bacilli were resistant to more than 500 micrograms of streptomycin per cubic centimeter. On the other hand, there was little change in the excretory or retrograde urograms.

It was the opinion of the joint committee that while these results seemed hopeful, only time could tell whether improvement in the lesions of the lower urinary tract would be permanent. The lack of change in the urograms should be noted. In a more recent report the Committee is more optimistic regarding the favorable effects of streptomycin in genito-urinary tuberculosis.

Army Experience. The 46 cases of proven genito-urinary tuberculosis observed in the Army streptomycin program were men of military age. In 18 cases there were tuberculous lesions elsewhere in the body, generally in the lungs. The course of treatment was adapted to the case. At the conclusion of treatment 11 patients were regarded as benefited and 11 as not benefited, while in 24 cases the results were too equivocal to permit any conclusions as to the value of streptomycin in tuberculosis of the genito-urinary tract.

Improved Group. Four of the 11 patients who were regarded as improved at the end of treatment had tuberculosis apparently confined to the bladder and seven others had tuberculosis of the bladder and kidneys; three patients in the latter group also had tuberculous epididymitis.

Only one of four patients whose tuberculous lesions were confined to the bladder had pulmonary tuberculosis; it was declared inactive. All were given 2 Gm. of streptomycin intramuscularly daily in five doses, over a period of 60 to 80 days. These patients had nephrectomies for tuberculosis prior to streptomycin therapy, with persistent draining sinuses in one. Cystoscopies showed multiple ulcerations of the vesical mucosa. In all patients relief from frequency and dysuria occurred progressively after two weeks of streptomycin therapy and vesical capacity increased significantly. Cystoscopy revealed progressive healing of the vesical lesions. The draining sinus after nephrectomy, present in one patient, closed during streptomycin treatment and remained healed. Other signs of improvement were negative smears and cultures and patients were observed for six months after the conclusion of treatment. There was a return toward normal limits of erythrocyte sedimentation rates. There was no clinical or bacteriologic evidence of relapse. Three of the four patients showed a significant gain in weight.

The six patients with vesical involvement and other lesions in one or both kidneys, who were regarded as improved, received streptomycin for an average of 120 days by the above dosage. A 31-year-old male with right renal and vesical tuberculosis showed symptomatic and cystoscopic evidence of improvement of vesical tuberculosis. Retrograde uograms, however, showed no improvement of the right kidney after 12 weeks of therapy, and the cultures were positive for acid fast bacilli resistant to streptomycin. Therefore, a right nephrectomy was performed. Examination of the kidney showed no change which could be attributed to streptomycin. The wound healed primarily. Streptomycin was discontinued six weeks postoperatively. The patient's condition at present is good. Each of the six patients had a similar clinical course; cystitis and dysuria were improved, the ulcerated lesions in the vesical mucosa disappeared, and urines became negative for acid-fast bacilli. There was, however, no change in the radiographic appearance of the kidney. Three patients had tuberculosis involving the bladder, ureter, one kidney, testicle and epididymis. Streptomycin was given two weeks before and six weeks following removal of the involved kidney, ureter, testicle and epididymis. In all instances the therapy appeared beneficial. The wounds and scrotal sinuses healed primarily and the cystitis cleared. Several cultures of the urine were negative for acid-fast bacilli, during the follow-up period.

Doubtful Group. The 24 patients with genito-urinary tuberculosis who had doubtful results from streptomycin fell into three classes. Four patients submitted to epididymectomy and/or orchectomy for tuberculous epididymitis and/or orchitis received streptomycin postoperatively in daily dosages of 2 Gm. The wounds healed primarily in three out of the four cases. Six patients with unilateral tuberculosis of the kidney were treated before and

after nephrectomy. The wounds healed primarily and the cystitis subsided. In the six cases followed there was no breakdown of wounds during a four-month period of observation, and no evidence of spread of the disease by the operation. The 14 doubtful cases of the third class received no genito-urinary surgical therapy. These cases had both kidneys involved, tuberculosis of a remaining kidney, or scrotal and testicular tuberculosis.

Unimproved Group. Of the 11 patients which were not benefited, nine received 1 Gm. or less of streptomycin per 24 hours; one had pulmonary tuberculosis; and one had tuberculous epididymitis.

Comment. This series of cases of tuberculosis of the genito-urinary tract is too small to be of any statistical significance. The fact, however, that only 11 of 46 patients improved on streptomycin therapy is not promising. It is probably important that most of the patients in whom improvement was observed had tuberculosis of the bladder or a scrotal sinus and that, in those in which other organs of the genito-urinary tract were involved, improvement was confined to the bladder or scrotum, the disease in the other organs showing practically no alteration. This suggests that streptomycin may be useful in the preoperative and postoperative management of cases of genital tuberculosis in which excision of the focus is undertaken. Per primam healing in tuberculous subjects is not readily achieved but was accomplished in a number of cases in this series under streptomycin protection.

The value of our data is diminished by an inadequate follow-up period and by the fact that removal of a tuberculous kidney will often, in itself, diminish a tuberculous cystitis. It appears that streptomycin without nephrectomy has not been given an adequate trial in unilateral tuberculous nephritis. Improvement has followed use of streptomycin for bilateral tuberculous nephritis and tuberculous cystitis.

The following are considerations for the use of streptomycin in tuberculosis of the genito-urinary system:

1. To be given prophylactically before, during, and after operations on infected organs to prevent wound-infection;
2. To be given for a draining tuberculous sinus, assuming that the main focus of infection has been resected;
3. To be given for tuberculous cystitis;
4. When the renal infection is accompanied by moderate pulmonary tuberculosis the genito-urinary infection is especially resistant to streptomycin;
5. The dose of streptomycin should not be less than 2 Gm. q.d. (as 0.5 Gm. q. 6 h.)

TUBERCULOSIS OF BONE

Up to June 1, 1948, 24 patients with tuberculosis of various bones (18 of the spine, six of the extremities) had been treated with streptomycin in Army general hospitals.

As of April, 1948, 192 patients with tuberculosis of various bones, including the vertebrae, were under treatment with streptomycin in Government

hospitals. The results showed a slow but appreciable improvement in a majority of the tuberculous lesions of bone and joints.

In 20 of the 24 patients treated with streptomycin in the Army program, culture, tissue sections, or both, revealed *Mycobacterium tuberculosis* as the etiologic agent. In the remaining four cases, there was clinical and roentgenologic evidence of the disease. The patients, who ranged in age from 18 to 38 years, were chiefly young men who were on active duty or who had just been separated from service when the disease was first noted. Fifteen of the 24 were white, seven were Negroes and two were yellow.

Eleven patients, eight with tuberculosis of the spine and three with tuberculosis of bones of the extremities, had pulmonary lesions, chiefly inactive, at the time of treatment. Two patients with tuberculosis of the spine also had tuberculosis of bones of the wrist and hand, respectively, and another had tuberculosis of the knee joint with sinus formation. One patient with tuberculosis of the elbow had an active tuberculous peritonitis. Soft tissue lesions were associated with the bone lesions in all cases. The average duration of illness before therapy was 14 months.

Six of the 24 cases showed some improvement in the status of the bone lesion after streptomycin therapy. Seventeen bony lesions were unchanged roentgenologically and one showed progressive destruction while on the antibiotic regimen. Eighteen associated soft tissue lesions were markedly improved, three were questionable and two were unaffected.

The results seemed to bear some relation to the status of the patient at the time treatment was begun. In chronically ill patients the average time for response to therapy was 69 days. In patients with subacute disease it was 51 days and in patients in good condition it was 37 days. One patient in excellent condition at the beginning of treatment showed no response at all to therapy and two patients, both chronically ill, developed tuberculous abscesses while under treatment.

Tuberculosis of the Spine. The 17 patients with tuberculosis of the spine (Pott's disease) had involvement of a single vertebra in one case, of two vertebrae in 11 cases, of three vertebrae in three cases, of six vertebrae in one case, and of seven vertebrae in one case. In four instances there were other distinct manifestations of tuberculosis of the bone. Fifteen of the 17 patients had adjacent paravertebral abscesses and four had other cold abscesses in distant locations.

Thirteen patients received streptomycin 2.0 Gm. daily for periods ranging from 38 to 140 days; four of these were treated 120 to 140 days. Two cases received 1.0 Gm. for 120 days and the remaining two cases were given 2.4 Gm. for 49 days and 3.0 Gm. for 91 days, respectively. In all instances streptomycin therapy was carried out in association with such standard measures as bed rest, the application of casts, blood transfusions, heliotherapy, and high-vitamin, high-caloric diets. Aspiration of the lesion was carried out in ten cases, incision and drainage in seven cases, spinal fusion in seven cases.

sequestrectomy in two cases and lobectomies including a right pneumonectomy in two cases.

Results. The response to streptomycin therapy in 17 cases of Pott's disease was regarded as good in three, fair in 11, and poor in three. The good results included arrest of the disease process in the bone with signs of recalcification by roentgen-ray, loss of pain and increase in the range of motion of the involved joints, early healing of the longstanding soft tissue lesions and marked improvement in the general well-being of the patient.

The responses to drug therapy listed as fair in the cases analyzed manifested roentgenologic evidence of no further progress in the disease of the bone, a successful fusion, rapid healing of the soft tissues which averaged 16 days and an improvement in the general condition of the patient.

The three cases listed as poor results showed roentgenological evidence of progressive bony destruction with little or no tendency for the soft tissue lesions to heal during the 120 days of treatment.

The seven spinal fusions carried out in this series of patients were all eventually successful. In the four cases in which fusion was carried out in the third or the fourth month, of streptomycin therapy, the postoperative course was uneventful. In three cases in which fusion was carried out without such protection, the postoperative course was stormy and wound dehiscence with infection occurred in one case.

Tuberculosis of the Bones of the Extremities. Of the six patients treated with streptomycin for tuberculosis of the extremities two had lesions in the metatarsals, two the metacarpals with a second lesion in the tibia of one, in the remaining two patients involvement of the elbow joint and scapula respectively were present.

Five of the patients received 2.0 Gm. of streptomycin daily for an average of 90 days. One patient was administered 1.0 Gm. for 104 days. One case received in conjunction with his intramuscular course, local irrigation of a sinus tract with 1.0 Gm. daily for 205 days. Sensitivity to the drug was noted in all the patients on 2.0 Gm. daily doses. Manifestations were mild vertigo, headache, and cutaneous rash. In all instances accepted supportive measures were utilized. Sequestrectomy was performed in four instances, repeated aspiration in one and the local excision of tuberculous tissue in another.

Results. The response to streptomycin therapy in six tuberculous lesions of the extremities was regarded as good in three cases and fair in the remaining three.

The improved cases demonstrated arrest of the destructive process and the recalcification of the bone as seen by roentgenologic survey after 60 days of therapy. Soft tissue lesions healed during the first month of therapy. The cases graded as fair demonstrated no further bone destruction but no regeneration was noted. Soft tissue sinuses and abscesses healed within 35 days after the initiation of therapy. The motion of the joints involved increased in range and pain on motion disappeared. The general condition of the patient was improved.

Local irrigation of the sinus tract in one case was unsuccessful and surgical excision of the tract was required for closure of the lesion.

Sequestrectomy performed without the protection of streptomycin was unsuccessful. When performed in conjunction with the drug successful closure with grafted skin was obtained.

COMMENT

The results of streptomycin therapy in this small series of cases could not possibly be regarded as definitive though certain conclusions seem warranted. There is no doubt that this drug can influence favorably the equilibrium between soft tissue defenses and sinus tract formations. On the other hand, the fact that abscesses, unless they are aspirated or drained, show resistance to dissolution is no more unexpected in abscesses of tuberculous origin than in those of coccal origin. The fact that two patients in the series, while under treatment, showed improvement in the status of the bone may be merely coincidental but also raises the hope that follow-up observations may show bone response in other cases in which it was not immediately evident, or that larger doses of streptomycin may produce better results in this respect.

This series demonstrates again that streptomycin is a useful umbrella for the surgery of tuberculous lesions. Surgery had to be resorted to in numerous cases in this series, for the usual reasons, and osteomyelitis of the long bones with sequestra remains a surgical problem, but the use of streptomycin before and after operation seems to prevent complications and promote wound healing.

TUBERCULOUS PERITONITIS (ULCERATIVE TUBERCULOUS ENTERITIS)

Up to June 1, 1948, 16 patients with tuberculous peritonitis (ulcerative tuberculous enteritis) and one patient with non-specific mesenteric granuloma had been treated with streptomycin and fully studied in Army general hospitals.

Previous Government Experience. The previous experience with streptomycin-treated peritonitis in Government hospitals was with 27 cases, in 19 of whom good results were secured by the intramuscular administration of the drug, with complete relief of symptoms and disappearance of ascitic fluid whenever it was present. The conclusion was that, although the series was small, the definite and uniform good results obtained by this mode of treatment in respect to symptoms warrants continued use of streptomycin, and furthermore that the value of oral administration of streptomycin is worthy of investigation. It was noted that in the presence of continuing pulmonary infection the permanence of the effects of streptomycin on lesions of the alimentary tract were suspect, though this consideration in no wise lessened the usefulness of the drug for relief of symptoms.

Army Experience. Of the 17 cases of tuberculous peritonitis treated with streptomycin in Army hospitals, the diagnosis was confirmed in ten by positive cultures of tissue sections for acid fast bacilli. In six cases the diagnosis was made on the basis of the history, the clinical course, and laparotomy. In one case the history, clinical course, and findings at operation suggested tubercu-

lous peritonitis, but the diagnosis was not substantiated by culture or inoculation, and tissue sections of mesenteric lymph nodes showed epithelioid giant cell granuloma.

All patients but two, who were young females, were young men of military age. Practically all were described as undernourished, chronically or acutely ill, and progressively going down hill. All were extremely ill at the time streptomycin treatment was instituted. In 16 cases the duration of symptoms varied from 36 days to 16 months; in the 10th case the patient had been acutely ill only three days but a history of chronic illness of six years duration was obtained.

The dosage of streptomycin varied from 1.5 to 4.7 Gm. daily, administered in divided doses by the intramuscular route. Five of the 17 patients received 1.0 Gm. daily; 10 received 2.0 Gm., and two others from 2.5 Gm. and 4.7 Gm. daily. The duration of treatment extended from eight to 28 days in five patients, 60 days in five patients and from 90 to 120 days in seven patients. Five patients also received penicillin. Duration of therapy with various dosages has not exhibited any significant correlation with improvement in the treatment of this disease.

Streptomycin therapy was accompanied by the usual sanatorium supportive measures. Intestinal decompression was used on both prophylactic and therapeutic indications in a few cases. Laparotomy was carried out in 14 cases.

Results. Eleven of the 16 patients who had proven tuberculous peritonitis were regarded as markedly improved, three were regarded as slightly improved and three were unimproved. Results were determined chiefly on the basis of whether or not they could reasonably be attributed to the use of streptomycin. A patient was regarded as improved by the course of therapy if, following the administration of the drug, there was an early reversal of the downhill course, and if the convalescence was of a character which would not have been anticipated in the light of the disease process.

Improved Group. In the 11 patients of streptomycin-treated tuberculous peritonitis in which improvement was evident, the pattern in all was somewhat similar. The response to therapy was rapid in four patients, in one of which improvement was evident on the third day of treatment. In the majority of cases, however, the improvement occurred gradually over a period of 28 days. A fall in temperature occurred as early as the first three or four days of treatment, followed by symptomatic relief from abdominal cramps and pain, decrease in abdominal distention, a change in facies, and improvement in appetite. The fall in the sedimentation rate was less prompt.

The patients first ceased to lose weight and then began slowly to gain as appetite improved. The doughy consistency of the abdomen and the intra-abdominal masses resolved slowly, in two cases only after 90 days of therapy.

Ten of the 11 patients were subjected to laparotomy. Eight received streptomycin in 2.0 Gm. daily dosages immediately after operation and all had uncomplicated recoveries. The ninth patient, who had been submitted to entero-enterostomy for intestinal obstruction, was given 8.0 Gm. of strepto-

mycin daily by the intramuscular route, combined with penicillin, for 72 hours and then received 4.0 Gm. daily for the next 10 days. His postoperative course was febrile. Thereafter varied dosages of streptomycin were given but there seemed no definite correlation between the dosages of the drug and the febrile reaction. The temperature finally dropped to normal on the 22d postoperative day, after therapy was discontinued. Streptomycin might have been responsible since it was given in unusually large dosage. The remaining patient subjected to surgery did not receive streptomycin after operation, and three draining sinuses appeared in the operative wound. All had healed spontaneously before the patient was given streptomycin five months later for improvement of his general condition.

One case in the improved group is worthy of special mention: A 20-year-old woman was admitted with a history of chills, temperature elevations to 102°F., nausea, and vomiting. Abdominal symptoms and signs of pain, tenderness and distention gradually increased over a period of five weeks prior to admission. Penicillin and sulfadiazine were without effect, and pleural effusion developed while they were being given. The patient was in extremely serious condition. Streptomycin was given, 1.5 Gm. daily for 12 days, 3.0 Gm. daily for the next 11 days, then 1.5 Gm. for another four days. At this time the drug was discontinued because of complaints of headache, nausea, dizziness and clouded vision. Three days after streptomycin therapy had been instituted, however, the temperature returned to normal limits, abdominal pain was less acute, and nausea and vomiting ceased. There was a weight gain of eight pounds while on therapy. Two weeks following the cessation of streptomycin patient was allowed to go home.

Questionable. The three patients considered to have a questionable response to streptomycin had in common symptomatic relief of abdominal pain, nausea and vomiting, and a slight but inconstant increase in appetite and weight. They are listed as doubtfully benefited because of a diminished yet persisting intra-abdominal mass and a doughy consistency of the abdomen after 120 days therapy.

Unimproved. Of the three patients considered unimproved two died. The third, not definitely diagnosed as tuberculosis, showed no improvement. The first failure, a 34-year-old white male with active pulmonary lesions and a widespread peritoneal involvement progressed rapidly downhill in the face of 120 days of streptomycin and a total dosage of 240 Gm. Oral streptomycin, 1.0 Gm. daily, seemed to relieve the nausea and diarrhea during the month just prior to death.

The second failure was in a 24-year-old white male with a 13-month history of constipation and a "swelling" of the right lower quadrant of the abdomen. A pleural effusion was demonstrable. Laparotomy revealed plastic tuberculous peritonitis. Numerous episodes of intestinal obstruction were relieved by decompression with the Miller Abbott tube. Malnutrition with progressive secondary anemia were present and repeated blood transfusions were necessary. Streptomycin was started, 4.0 Gm. daily intramuscularly,

together with penicillin in daily dosages of 240,000 units. At the end of four days the temperature fell to normal limits, but there was no improvement in the clinical course and death occurred after 16 days of streptomycin. Post-mortem examination revealed stenosis of the ileum with obstruction from plastic tuberculous adhesions. Streptomycin in this case was frankly a measure of desperation. No significant results were anticipated from its use and none were secured.

The third poor result was in a 28-year-old man who had become ill 12 months before he was treated with streptomycin. Shortly after the onset of symptoms (March, 1946) laparotomy was performed for intestinal obstruction complicated by peritonitis. Sinuses developed in the wound postoperatively and drained intermittently. Eight months after the first operation the abdomen was again opened to determine the character of a mass palpable beneath the sinus tracts. Exploration revealed an abscess communicating with the sinuses as well as partial intestinal obstruction from a plastic peritonitis. Coliform bacteria were cultured from the abscess. Entero-enterostomy was performed. Following this operation the patient had a number of febrile episodes and during May and June 1947, he received two courses of streptomycin, and five courses of penicillin. During the first course of streptomycin 11 Gm. were given over a 13-day period and during the second course 16 Gm. were given over an eight-day period, without any response. On July 1, 1947, elective laparotomy revealed an abscess in caseating nodes. All infected tissues were excised. Slight symptomatic improvement followed the administration of 2.0 Gm. of streptomycin daily for 25 days. The sedimentation rate and leukocyte count remained elevated and there was no gain in weight. Culture of the exudate from the abscess and the lymph nodes excised at the last operation revealed no acid-fast bacilli. Tissue section of the lymph nodes was reported as showing epithelioid cells, giant cells and necrotic debris but no tubercles, fungi or acid fast bacilli. The tuberculin test was positive only at 1:100 old tuberculin. The final diagnosis was nonspecific granuloma. This case emphasizes the need for accurate diagnosis if beneficial effects of streptomycin therapy are to be expected.

COMMENT

The 16 of 17 patients in this series with proved tuberculous peritonitis were all extremely ill when streptomycin therapy was begun. After therapy, 11 were markedly improved, four were slightly benefited, and three were unimproved. Two patients died. The series is small, but the results suggest that streptomycin is the drug of choice for the treatment of tuberculous peritonitis. There is no justification, however, for claiming that these patients were cured. The follow-up data are meager. Adults may present remission or arrestation of tuberculous peritoneal processes in the absence of specific therapy and later may present exacerbations of the disease or may die of tuberculous lesions elsewhere. It remains, therefore, for larger groups of tuberculosis of the peritoneum to be treated by streptomycin and to be fol-

lowed for periods of years before any conclusions as to the value of this agent for this condition can be defined. For the present time 1.5 Gm. streptomycin daily for 60 days would appear to be optimum treatment.

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SURGICAL REPAIR OF LACERATIONS AND FISTULAS OF THE PAROTID DUCT*

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RESULTS FOLLOWING SURGICAL REPAIR of laceration or fistula of the parotid duct so far have not been uniformly satisfactory. This has been true especially of attempts at repair in the more chronic types of fistula. The problem is one that may suddenly confront any surgeon even though injury of the parotid duct occurs infrequently.

The authors have treated surgically five patients with lacerated parotid duct, in some cases the condition having been present for a few hours, in others a few weeks. In each case successful results were obtained by the use of a simple technic that will be described. No claim of originality is made since the main principles of the operation already have been applied by others.

ANATOMY

The parotid duct leaves the anterior border of the parotid gland and extends forward horizontally across the masseter muscle. It is accompanied by branches of the facial nerve and facial artery which usually are to be found running above the duct. The duct passes inward at the anterior border of the masseter muscle, piercing the layer of fat and the buccinator muscle. It then passes forward for about 5 mm., to emerge through a narrow opening in the papilla opposite the second upper molar tooth. The course of the duct will be roughly shown by drawing a line from the lower edge of the external auditory meatus to the upper border of the upper lip.

The duct is a fibrous tube about 6 cm. in length and 4 to 5 mm. in diameter. It ejects saliva during mastication by action of the contractile tissue in its walls. At the papillary end of the duct there is a sharp angulation that acts as a valve, preventing food from entering.

HISTORY

Prior to 1926 there were few reported cases in which anastomosis of the parotid duct was made. Schmieden,¹ in 1916, reported such a case but gave no description of the technic used. Since 1926 there have been occasional reports of duct repair but in each instance the series of cases has been too small to allow any definite conclusions regarding the method used. In reviewing the various technics described it is evident that the use of a dowel to splint the duct has been generally accepted. Tees,² in 1926, reported two cases in which a strand of catgut was used to serve as a dowel over which the duct was approximated by means of two fine, interrupted catgut sutures passed through

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the sheath. He advised leaving the catgut entirely within the duct. Dickinson,³ in 1927, used a strand of silkworm gut which was allowed to project into the mouth. He fixed the strand at its point of entrance into the mouth by a suture. Black and Flagge,⁴ in 1928, used a small ureteral catheter to act as a dowel, leaving about 1 inch of the catheter extending into the mouth. Butler and Guinan,⁵ in 1933, also used a ureteral catheter as a dowel, anchoring it to the canine tooth of the upper jaw with a silk ligature. Brohm and Bird,⁶ in 1935, brought the dowel out through the cheek and sutured it to the skin. Newman and Seabrook,⁸ in 1946, reported the use of tantalum wire as a dowel, bringing it out of the mouth and taping it to the cheek. Fixing the dowel in the duct has been the most difficult problem. In the technic used by the authors this difficulty has been removed.

GENERAL CONSIDERATIONS IN TREATMENT

Injuries of the parotid duct and gland may occur in one of three areas: (1) over the parotid gland, (2) over the masseter muscle, and (3) in the buccinator muscle area.

Fistula of the glandular area. Many fistulas of the smaller ducts of the gland will heal spontaneously. Roentgen therapy and cauterization of the wound sometimes will produce healing. Fistula in the larger ducts of the gland may be treated in the manner to be described.

Fistula over the masseter muscle. The majority of parotid duct fistulas occur in this area and can be treated easily and quickly by the technic described in this paper.

Fistula in the buccinator area. Injuries in this area often have been treated by short-circuiting operations that cause the saliva to flow into the mouth proximal to the papilla. This method does away with the valve-like action of the papilla and there is no protection against ascending infection from the mouth. The authors believe that every attempt should be made to preserve the papilla. The technic used by us was found to be satisfactory in repairing lacerations in the buccinator area.

TECHNIC

Preoperative. Good oral hygiene should be maintained and a mouth wash used every two hours, beginning immediately after the diagnosis is made and continuing until the time of operation. Penicillin may be used intramuscularly for 24 hours before surgery.

Operative. After the skin has been cleansed and a mouth wash used, the face is draped. Local anesthesia then is injected into the skin surrounding the laceration or fistula. An incision about 1½ cm. in length is made through the skin, care being taken to avoid the nerves and vessels that lie next to the duct. A probe is then passed through the mouth, into the papilla and along the duct toward the incision. The end of the probe is brought out through the incised wound and a strand of cotton thread size No. 10 (or heavy silk) is fastened to it. The threaded probe is then pulled back through the duct into

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the mouth. The patient is given a few drops of lemon juice to stimulate the salivary flow. It is then usually easy to identify the proximal end of the severed duct in the incision. The end of the cotton or silk strand is threaded

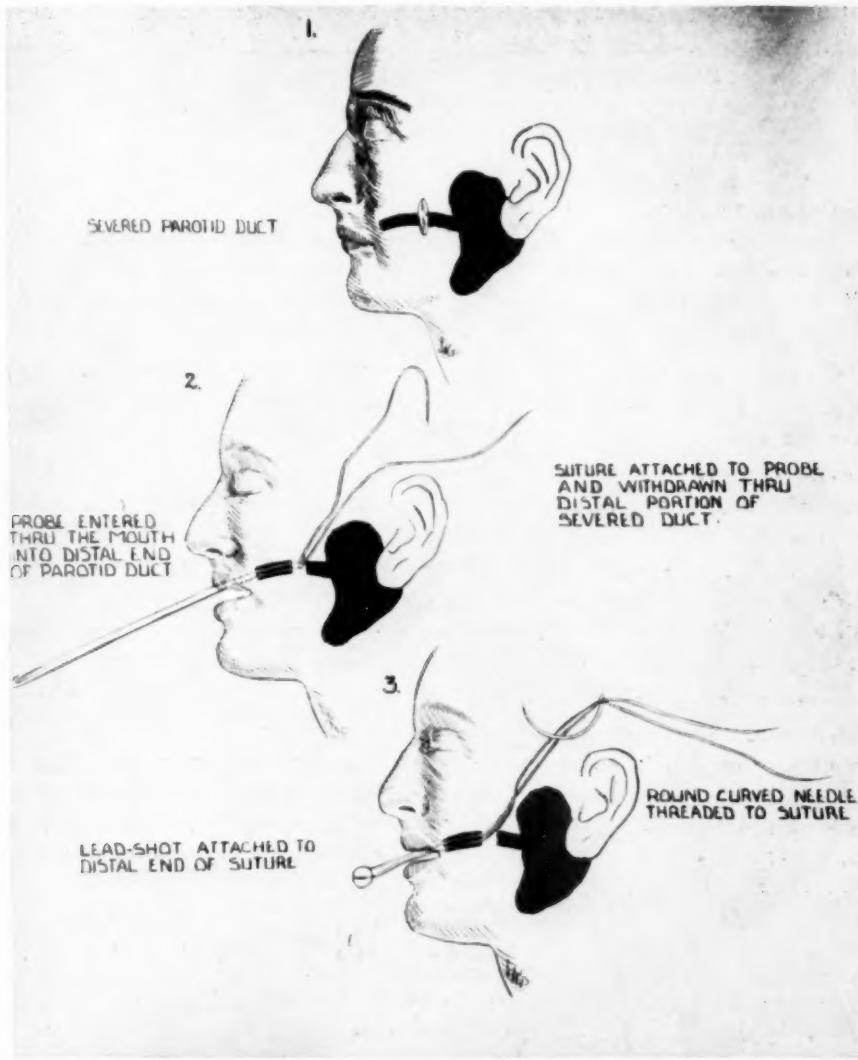


FIG. 1.—First 3 stages of repair of parotid duct.

on a long Mayo needle and the needle passed backwards, blunt end first, into the proximal duct. With gentle manipulation the needle is forced through the parotid gland to the skin. A tiny nick is made in the skin and the thread carried through (Fig. 1).

A lead shot applied to each end of the thread holds it snugly in place. A small square of rubber sheeting inserted between the mucosa and the lead pellet will prevent irritation.

The tissues in the incision are approximated with interrupted catgut sutures and the skin closed without drainage (Fig. 2).

Postoperative Care. The patient should continue to use a mouth wash frequently. His oral hygiene must be supervised carefully and fluids given

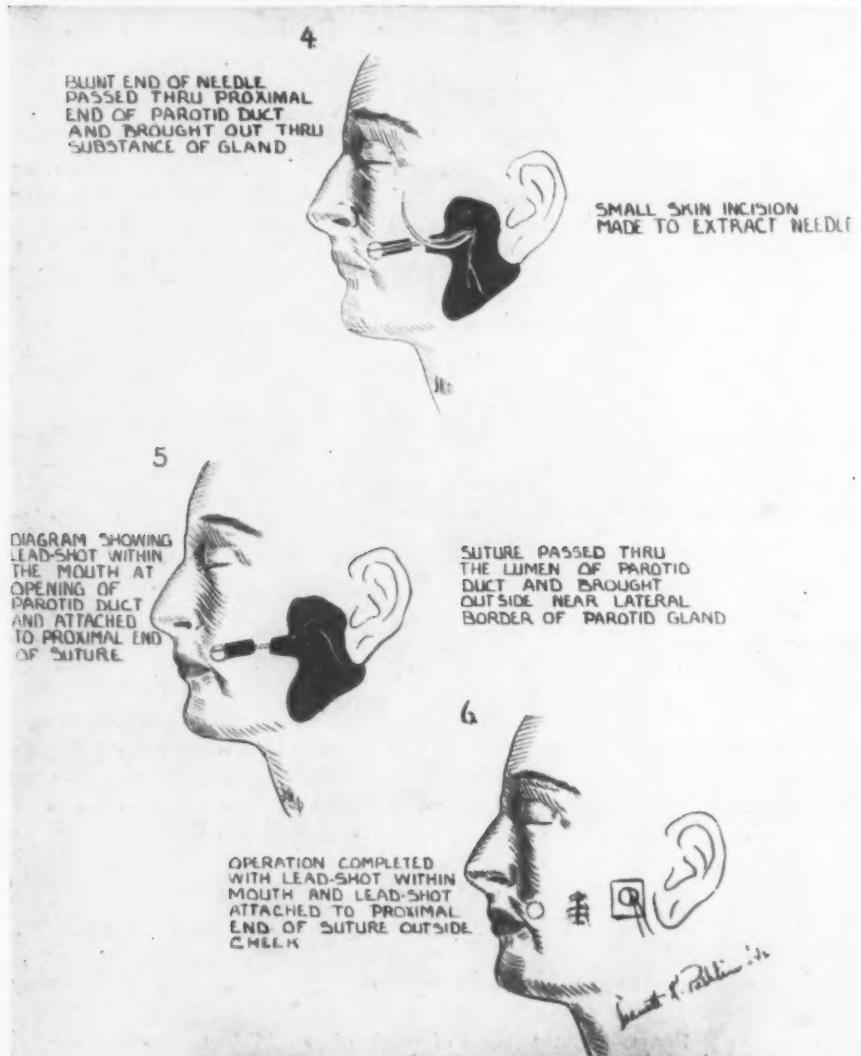


FIG. 2.—Last 3 stages of repair of parotid duct.

freely. Penicillin may be given intramuscularly for several days following operation. As a rule, a watery fluid will drain from the incision for about a week. Swelling that is not of inflammatory origin may be disregarded.

The sutures usually are removed from the wound at the end of seven days. The cotton or silk dowel should not be removed until the 14th postoperative

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day. Salivary juices usually enter the mouth through the duct soon after operation, and it will be noted by the patient that the buccal mucosa on the injured side no longer is dry.

CASE REPORTS*

Case 1.—D. H., white, male, age 28, received treatment July 11, 1942, for numerous lacerations of the left side of the face and neck, also the left shoulder. When seen later (July 15), there was moderate swelling of the left side of the face. The patient stated that his dressings became soaked with a water-like substance when he ate. A diagnosis of laceration of the parotid duct was made. Warm compresses were applied to the inflamed area for several days but the drainage persisted. Operation for the repair of the lacerated duct was performed July 21, 1942, using the technic described. Postoperative treatment consisted of sulfathiazole, a perborate mouth wash at regular intervals, and a liquid diet. The swelling of the left cheek persisted for three days. At the end of this period saliva began entering the mouth freely. The suture was removed August 14. The patient was discharged six days later, the gland and duct functioning normally.

Case 2.—A. M., colored, male, age 35, received a knife laceration of the left side of the face just in front of the ear. The wound was sutured by his local physician. One week later, according to the patient, a large tender mass was noted just anterior to the left ear. The patient stated that the mass increased in size on mastication.

Operation was performed Oct. 31, 1941, in accordance with the technic described. Saliva was seen coming through the duct into the mouth a few hours after operation. The patient was discharged Nov. 4, with a normally functioning duct. The suture was removed three weeks later. The wound had completely healed and no swelling was present.

Case 3.—R. T., colored, male, age 48, was admitted to the hospital after receiving multiple lacerations of the left side of the face and neck. The most severe of the lacerations extended across the left cheek from the side of the ear to the upper lip. The lacerations were sutured shortly after admission. Several days later prominent swelling of the left side of the face was noted. Fluid aspirated from the swollen area was found on examination to contain amylase.

Sixteen days after admission the divided Stensen's duct was repaired, employing the usual technic. The duct was found to be completely severed as was a small portion of the parotid gland itself. There was generalized oozing of saliva from the entire lacerated portion of the gland. Following operation the face remained swollen for a few days, a scant flow of saliva escaping through the incision. Approximately one week after operation the swelling had completely subsided, saliva flowing freely into the mouth. The suture was removed on the 12th postoperative day.

Case 4.—E. O., white, male, age 39, was admitted to the hospital complaining of a watery drainage from his left cheek at the site of a sutured laceration in this area received 20 days earlier. The patient stated that the drainage was most noticeable during meals.

Surgical repair of the lacerated duct was carried out Nov. 19, 1947, in accordance with the method described. Drainage from the incision ceased about the 4th postoperative day, saliva flowing freely into the mouth. The suture was removed on the 15th postoperative day, the parotid duct and gland having continued to function normally.

Case 5.—A. N., white, male, age 60, was admitted to the hospital August 1, 1945, with a tumor just anterior to the left parotid gland. The patient stated that the tumor had been present since about the time of the first world war. A mixed tumor 7 by 3 by 2 cm. was removed August 2, 1945. A few days later drainage from the operative incision was noted. A diagnosis of parotid duct fistula was made.

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Surgical repair of the fistula was carried out August 19, 1945, and the technic used was that suggested by the authors. The drainage from the previous operative incision ceased within a few days following repair of the fistula. When the patient was last seen both wounds were dry and well healed.

SUMMARY AND CONCLUSIONS

Salivary fistulas of the parotid duct and gland respond to treatment if certain principles are observed, the most important of these being the use of a dowel to splint the severed duct. A simplified method of anchoring the dowel is described. The duct papilla must be preserved if possible. Five cases in which successful results were obtained using the authors' technic are reported.

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ACUTE DIVERTICULITIS OF THE CECUM*

REPORT OF THREE CASES DIAGNOSED PRE-OPERATIVELY
AS ACUTE APPENDICITIS

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OUT-POUCHINGS OF THE COLON of various sizes, shapes, positions, and types occur very frequently throughout the population at large. The exact number can be only estimated because of the obviously large number which are never diagnosed. This is largely due to the fact that they cause no symptoms to necessitate the individual either being subjected to roentgenologic examination with a barium enema, or to gastro-intestinal studies as a result of abdominal complaints. Those found at autopsy represent a very small percentage of the total population. A few are found as incidental findings at operation. In routine autopsies, Mayo²⁵ reports from 5 to 7 per cent of all the colons examined revealed diverticula some place throughout their entirety. Epstein⁸ quotes Sprigg and Marker to show that out of 1,000 routine roentgen-ray examinations of the colon, 100 diverticula were found. The location of each showed about 58 in the pelvic colon, 46 in the descending colon, 16 in the transverse colon, 10 in the ascending colon, 7 in the cecum, 5 in the appendix, and 3 in the rectum. Anderson¹ reports a 5.7 per cent occurrence of the diverticulosis of the colon noted in routine roentgenologic examinations, and 6.9 per cent occurrence of diverticulosis in routine autopsies.

Diverticulosis is the term used to denote those silent out-pouchings of the colon with small necks and lined by mucosa, in which there is no evidence of inflammation or symptoms referable thereto. When these blind sacs become inflamed, either because of obstruction or other causes, the diagnosis of diverticulitis must be made. Bennett and Jones⁴ estimate that in only 12 to 15 per cent of the cases of diverticulosis, does inflammation occur to justify the diagnosis of diverticulitis. Ochsner and Bargen¹⁹ found that in 2 per cent of 151 cases of uncomplicated diverticulosis of the colon, the diverticula were present in the right half of the colon, and that about 14 per cent of all diverticula become inflamed, and 15 per cent of these inflamed diverticula were subjected to surgery. From this it is seen that acute diverticulitis of the cecum meriting surgical intervention is not a rare condition. Various authors have reported and reviewed cases appearing in the literature since the first case was reported by Patier in 1912. In 1944, Noon and Schenk²⁷ reported 48 cases and added three of their own. These cases were taken from the American and British literature and represented the highest number of cases noted to that date until Anderson's¹ recent, most comprehensive review, in which 91 cases of acute diverticulitis of the cecum were reported from the literature. To

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these he added nine cases. These nine cases of acute diverticulitis of the cecum were among some 700 cases of surgical diverticula of the colon at the Mayo Clinic.

The three cases of acute diverticulitis of the cecum herein presented were seen on the surgical service of this Veterans Administration Hospital within a 12 months' period; all three were diagnosed preoperatively as acute appendicitis; all were subjected to surgery. An acutely inflamed true diverticulum was found in each, and in two cases rupture of the diverticulum with abscess formation was encountered. These cases will bring the total of those reported to over 100, and will help to disprove the previously held belief that this is a rare surgical entity, and should impress the surgeon that it is one which must be kept constantly in mind when the diagnosis of right-sided abdominal pathology is made preoperatively. It also must be considered when the pathologic condition of the appendix found at operation is not sufficient to explain the signs and symptoms leading to preoperative diagnosis of appendicitis.

In a patient presenting signs and symptoms characteristic of appendicitis, in whom an appendectomy has previously been performed, the diagnosis of acute diverticulitis of the cecum must be considered as a very real possibility.

The average age incidence of this disease is given by different authors to be approximately 40 years. In our cases, all the patients were males due to the character of the hospital in which the cases were seen. Their ages were 25, 35 and 30, respectively. It has been noted in the past that there has been a preponderance of males reported with this condition. However, Anderson¹ finds about an equal number of each sex with this disease.

The cause of diverticulosis and subsequent diverticulitis is not definitely established, but Greensfelder and Hiller¹⁵ suggest that any one, or several, of the following mechanisms may be important as a causative agent: (1) eversion of the cecal wall between two constricting bands, (2) traction by abdominal adhesion (usually postoperatively), (3) eversion of a weak spot in the cecal wall, caused by migration of a purse string suture into the lumen of the intestine (postoperatively), (4) eversion of the weakened area in the cecal wall, resulting from the rupture into the cecum of an abscess of the appendiceal stump, (5) weakening of the wall of the bowel at the site of entrance of blood vessels into the muscularis, (6) increased intraluminal pressure in the cecum, either due to constipation or increased intraabdominal pressure, (7) inherent weakness of the wall of the bowel due to age, congenital weakness, obesity or atrophy of the fat along the vessels which penetrate the wall, (8) traction on appendiceal epiploicae, mesentery or omentum, with or without adhesions, (9) traumatic diverticula following previous operative procedure, especially appendectomy (this type is classified as "Secondary Diverticula"), (10) retention in residual form of the appendix which appears in embryologic life but normally disappears before the true appendix develops, (11) cathartics, etc.

The preoperative diagnosis is, in the great majority of the cases, acute appendicitis and operation is carried out for alleviation of that condition. The following preoperative diagnoses have been made: Acute appendicitis, gan-

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grenous appendicitis, perforating appendicitis, appendiceal abscess, subacute appendicitis, chronic appendicitis, uterine fibroid (degenerated), salpingitis, carcinoma of the cecum, diverticulitis of the right colon, obturator hernia, stump appendicitis, abscess of undetermined origin and benign ulcer of the cecum.

In approximately one-third of the reported cases, histories of previous attacks of right lower quadrant pain were elicited. The most usual complaint of patients is pain in the right lower quadrant, either localized or generalized. Pain may be of a cramping or dull aching type and it was present in various patients for periods of a few hours to several days. The general observation has been made by several observers that in acute diverticulitis of the cecum, the pain is less severe and more prolonged, and shows a more chronic course in contradistinction to acute appendicitis where the pain is more acute, and of shorter duration. However, this is purely an impressionistic finding. Other symptoms noted with more or less frequency are: Tenderness in the right lower quadrant, mass in right side of the abdomen, rebound tenderness, psoas tenderness and tenderness over the entire abdomen.

The differential diagnosis, preoperatively, is not easy because of the many diseases which this condition resembles. When a diagnosis of an acute surgical condition in the abdomen is made, roentgen-rays are of little value and are contraindicated. The laboratory work has proven to be of very little help in differential diagnosis, as the same picture is noted here as is noted in acute appendicitis. A leukocytosis may or may not be present. Usually there are no urinary findings which are of any help. Also, if roentgen-ray examination of the colon were made, it would be ineffective in demonstrating diverticula which are plugged by feces, fecoliths, or pus, causing visualization to be impossible. Thus, it is seen that a differential diagnosis of acute diverticulitis of the cecum as against acute appendicitis cannot be made, but it is a condition which should constantly be kept in mind by the diagnostician and operating surgeon.

Diverticula may be divided into two groups. True diverticula are those in which all normal layers of the intestine, including the mucosa, submucosa, muscularis, and serosa are present over the entire diverticula, the false or acquired type are those in which the muscularis is absent, the other layers being present. It is believed that false diverticula represent out-pouchings through weak points in the muscularis of the bowel. The true diverticula are probably congenital. All three of the cases here reported were true diverticula, as shown by the presence of all layers on microscopic pathological examinations. Diverticula in the cecum, when present, are usually not associated with the presence of diverticula throughout the remaining portion of the large bowel. The majority of those cases reported are the true type and are solitary. Two of the cases here reported are true solitary diverticula; the third is a true type but multiple.

CASE REPORTS

Case 1: A 25-year-old white male entered the hospital on June 13, 1946, with a history of abdominal cramps of 48 hours' duration, most marked in the right lower

quadrant and slight nausea over the same period of time. There was no vomiting, diarrhea or increase in temperature noted by the patient. On examination, generalized abdominal tenderness was noted, which was localized and most marked in the right lower quadrant. Slight rigidity and slight rebound tenderness were noted in the right side of the lower abdomen. Rectal examination revealed no mass, but some tenderness in the right lower quadrant was present. The leukocyte count showed 13,200 cell per cubic mm. of blood with 62 polymorphonuclear leukocytes. The examination of the urine revealed no abnormal findings. His admission temperature was 99.5°F. A preoperative diagnosis of

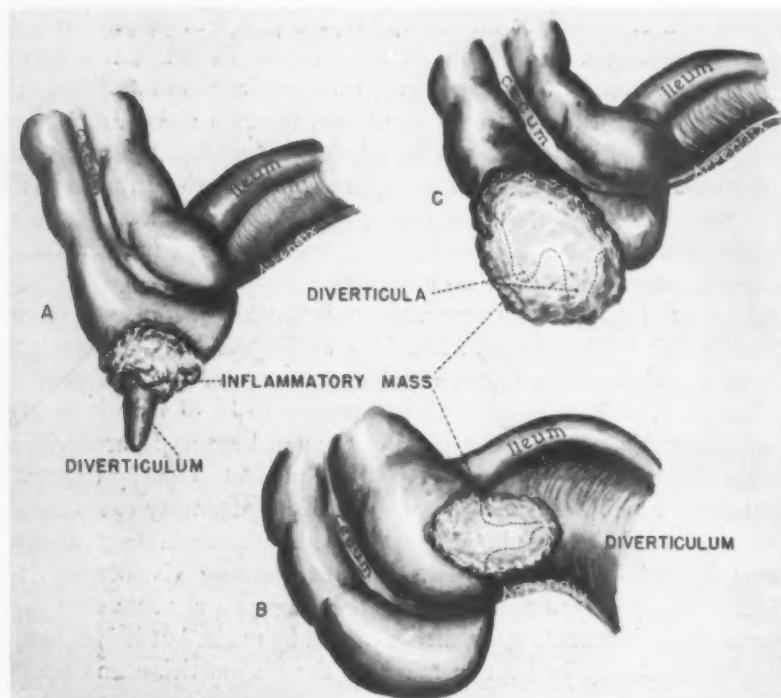


FIG. 1.—A. illustrates the location and appearance of the lesion in Case 1—an inflammatory mass at the base of the diverticulum without perforation.

B. shows the perforated diverticulum within an inflammatory mass—
involving the meso-appendix encountered in Case 2.

C. double diverticula within a walled-off abscess as seen in Case 3. One of the diverticula is perforated at its tip.

acute appendicitis was made. At operation, which was performed by Dr. D. J. Abramson, the appendix was found to be in a normal position and not inflamed. There was a mass, measuring 3 by 4 centimeters in the redundant portion of the cecum. This mass was located opposite the ileo-cecal valve on the anterior lateral aspect of the cecum, near the free tenia of the colon (Fig. 1A). On careful investigation, this mass was found to have in its center a markedly inflamed diverticulum of the cecum containing a fecalith and a considerable amount of fibrinous exudate at its base. The diverticulum, which was not perforated, was amputated at its base and the defect in the colon closed with purse-string type inverting cat gut suture in the serosa and this was reinforced by interrupted sutures. The appendix, which was not abnormal, was also removed. The abdomen was closed without drainage and without chemotherapeutic agents in the peritoneal cavity. The convalescence was uneventful and the patient was discharged from the hospital 8 days later. The

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pathological examination showed a marked inflammatory process throughout the wall of a true diverticulum which contained mucosa, muscularis and serosa. The appendix showed no pathologic changes. Follow-up barium enema studies of the colon revealed no further diverticula.

Case 2: A 35-year-old white male admitted to the hospital February 13, 1947, with the complaint of abdominal pain, aching in character, which has been present in a mild degree intermittently for several years. The day before admission, the pain became much worse and was confined predominantly to the right lower quadrant. He noted no radiation of the pain. There was no vomiting or nausea. He had a history of normal bowel



FIG. 2.—X-ray examination of colon with barium enema showing one additional small diverticulum on the medial aspect of the ascending colon near the hepatic flexure.

movement on the day previous to admission. He felt some burning on urination but no other prominent genito-urinary symptoms. His temperature on admission was 98.6°F. Examination revealed marked tenderness in the right lower quadrant, slight rigidity, moderate rebound tenderness with a positive psoas tenderness noted in the right lower quadrant. Laboratory findings on admission revealed a white blood cell count of 11,250 per cubic mm of blood, with 69 polymorphonuclear cells. The urine examination was negative. A preoperative diagnosis of acute appendicitis was made. The operation, which was performed under spinal anesthesia, was carried out through a McBurney type incision. There was no free fluid present. Upon mobilization of the cecum, the appendix was noted to be greatly elongated but not markedly inflamed. At a point about one-half inch distal to the appendix on the medial aspect of the cecum, there was a large firm inflammatory mass the size of a hen's egg involving the meso-appendix (Fig. 1B). This mass

was carefully dissected from the cecum along its serosal covering and a gangrenous diverticulum was noted. This gangrenous mass was tightly adherent to the cecum and was made up of inflammatory tissue covered tightly by meso-appendix and in its center was the perforated tip of the diverticulum. The entire mass was excised at the base of the diverticulum. The defect in the cecum was closed with interrupted catgut sutures and reinforced with #60 cotton sutures. There was no spillage into the peritoneal cavity and no evidence of generalized peritonitis. The appendix was removed routinely. The abdomen was closed without drainage and without the institution of chemotherapy. The patient's convalescence was not remarkable and he was discharged from the hospital 15 days postoperatively. Roentgen-ray study of the gastro-intestinal tract and a barium enema examination of the colon postoperatively revealed no evidence of diverticula throughout the rest of the colon. Pathologic examination revealed a small sac-like structure which contained many blood vessels, eosinophils, polymorphonuclear and lymphocytic infiltration throughout the walls; layers of muscularis, mucosa and serosa were noted and a diagnosis of gangrenous diverticulum was made.

Approximately two weeks following the patient's discharge from the hospital, he was readmitted with complaints of fever, chills and swelling in the right lower quadrant. Physical examination at this time revealed a tender, firm mass beneath the recent McBurney scar. Temperature was 101.4°F. on admission. Examination was otherwise negative. After conservative treatment with wet packs and chemotherapy for a few days, the mass was opened surgically under sodium pentothal anesthesia and was found to be a subcutaneous hematoma. This was drained and no evidence of inflammation, exudate or pus was noted. Patient was discharged 20 days later, completely well.

Case 3: The patient was a 30-year-old white male who entered the hospital on May 20, 1947, with a history of awakening in the morning with soreness in the right lower quadrant which continued without relief up until the time of examination. There had been no nausea or vomiting. His bowels had moved normally the day before. He had had no history of similar attacks; no hematemesis, jaundice or other G.I. complaints. He had a history of recurrent attacks of malaria since his discharge from the service. His temperature on admission was 99.6°F. Examination revealed moderate tenderness on deep palpation in the right lower quadrant with rebound tenderness referred to McBurney's point. There was no spasm and no palpable mass. Urine examination, on admission, showed an occasional coarse, granular cast; otherwise it was negative. Subsequent urine examination showed an occasional hyaline cast, another coarse granular casts, from 5 to 6 white blood cells, and 10 to 12 red blood cells per high power field. His serology was negative. Examination of his blood showed a white blood count of 12,400 cells per cubic mm. of blood with 75 polymorphonuclear cells. A diagnosis of acute appendicitis was made. The operation was carried out under spinal anesthesia through a transverse incision in the right lower quadrant. There was no free fluid present in the peritoneal cavity. A firm mass, the size of a hen's egg, was found bound down in the right gutter on the lateral aspect of the cecum (Fig. 1C). Inspection revealed the appendix to be lying free and not involved in the mass and not inflamed. The cecum was mobilized with difficulty, and the cecum and mass exteriorized. The mass was dissected from the cecum and in its center was found a ruptured diverticulum with abscess formation. The appendix was somewhat inflamed. The diverticulum was on the posterior lateral aspect of the cecum, approximately 1½ inches lateral to the base of the appendix. It had a broad base and its tip was divided to form two separated diverticula, one of which was inflamed and the other of which was perforated and involved in the before-mentioned mass. The wide base of the two diverticula was clamped, the mass excised, and the defect in the cecum closed with an inverting type of catgut suture reinforced by #40 interrupted cotton sutures. The appendix was removed in the routine manner. Inspection of the remaining exposed portion of the colon revealed no further diverticula. The abdomen was closed without drainage and no chemotherapy instituted. The pathologic examination

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showed the specimen to be a true diverticulum containing all layers of small intestine with necrosis of the epithelium and diffuse invasion of the wall by leukocytes in the muscularis. Convalescence was uneventful and the patient was discharged approximately 17 days postoperatively. At this time a gastro-intestinal roentgenographic study was made, as well as a barium enema examination which revealed a small diverticulum on the medial aspect of the ascending colon, just below the hepatic flexure (Fig. 2). There was no other evidence of diverticula or pathology.

COMMENT

It is seen from these cases that acute diverticulitis of the cecum closely resembles an acute appendicitis in all respects and behaves very similarly in the abdomen. Abscess is usually formed at the site of perforation and very rarely causes generalized peritonitis. The omentum frequently acts to localize the exudated material and holds it in check to form abscesses similar to those noted in two of these cases. The abscesses often lie adjacent to the mesentery or between its leaves. These thick-walled abscesses are closely associated with the cecum and often become tumefied and associated with large mesenteric lymph nodes to the extent that differential diagnosis of malignant tumors of the cecum is very difficult, if not impossible, even at operation. This is a very important fact because, as is well known, carcinoma of the cecum is much more common than diverticulitis of the cecum. Consequently, unless the accurate diagnosis is made by the operating surgeon, the improper operative procedure may be carried out and a radical resection of the cecum and ascending colon done in the belief that the lesion at hand is a carcinoma, whereas in reality it may be an inflamed diverticulum and a simple resection of the local lesion is all that is necessary. On the other hand, since diagnosis of carcinoma of the cecum is a much more formidable one and the sequelae carry such a high mortality, error in the opposite direction should also be guarded against. Most patients subjected to surgery for diverticulitis of the cecum recover. The mortality rate is given as 6 per cent.

At operation the usual finding is a single diverticulum with a narrow neck in the outer portion of the cecum. It may have become congested by concretions or fecalith and obstructed and the neck traps pus in the blind sac. Since the muscularis is often absent or very deficient there is no pressure to force the fecalith or blocking concretion out of the neck and thus obstruction and strangulation result. This set of circumstances differs from the normal functioning appendix which is able, in numerous cases, to empty itself. Due to this bottle neck formation and stasis and an increased absorption of water in the right colon, fecaliths are more liable to form and give rise to acute inflammatory reaction here. Jonas¹⁶ found fecalith present in 68.4 per cent of his cases. A fecalith was present in only one of the cases reported in our series of three.

Local sequelae following acute diverticulitis of the cecum may be: (1) Perforation with localized or generalized peritonitis, (2) gangrene of the diverticulum, (3) abscess formation, usually involving the right portion of the cecum, peritoneum in the right lower quadrant, and omentum, (4) multiple adhesions in the area of the diverticula, (5) entero-intestinal fistula, or

entero-vesicle fistula, or entero-colic fistula, or others, (6) retrocecal abscess, (7) extra-peritoneal abscess.

There may be a diverticulitis with intestinal obstruction or there may be diverticulitis associated with a carcinoma of the cecum, so both should be kept in mind at the time of operation. Upon palpation of a mass in the cecum at the time of operation, an examining finger may be placed in the opposite wall of the cecum and the surgeon may feel a defect or hole in the mass at the site of the base of the diverticulum, and this may give some aid in differentiating it from a carcinoma.

The other diseases which must be considered and differentiated from acute cecal diverticulitis are: Acute appendicitis, carcinoma of the cecum, actinomycosis of the cecum and right side of the bowel, and intussusception.

The microscopic pathology usually noted is gangrene of the mucosa with ulceration, inflammation of the muscularis with thickening and edema, with infiltration of blood vessels, and increase in the leukocytes in the subserosa, as well as fragmentation of the muscularis, and a generalized inflammatory picture. Perforation is much more likely if the muscularis of the bowel is absent in the diverticulum proper.

The treatment should be such that the minimal operative procedure is carried out to effectively eradicate the pathology present. The plan of treatment necessarily depends on the type and extent of the lesion, as follows: (1) Simple excision of the involved diverticulum with closure of the defect in the cecum (similar to the procedure carried out in routine appendectomy) can be done if too much of the bowel wall is not involved. In this respect, our experience is compatible with that of Gatewood¹² in that the tissue edges of the bowel were normal despite the gangrenous character of the diverticulum itself, and closure of the cecal defect could be carried out with ease by a purse string-type suture. However, if edema and thickening of the cecal wall in the area of the diverticulum is marked due to abscess formation and gangrene, as reported by Frehling,⁹ closure of the cecal defect is difficult and more extensive resection of the cecum may be necessary to get an effectual closure. (2) Simple closure of the defect after a perforation has occurred by invagination of the stump and suturing normal serosa to serosa at the base of the cecum is simple and often adequate. (3) Right colectomy will be necessary if too much of the cecum and ascending colon is involved in inflammatory and gangrenous mass and it is evident that any lesser procedure would jeopardize the patient's welfare, or would add to the spread of infection or increase morbidity or mortality. This should be used as the last resort. However, Jonas¹³ points out that very large inflamed diverticula lying close to the ileo-cecal valve or between the leaves of the mesentery, so as to jeopardize the cecal blood supply, require extensive resection, including the terminal ileum and ascending colon, with an anastomosis between the ileum and transverse colon. (4) Drainage of an abscess is the only practical procedure when present, or an inflammatory mass adherent to the terminal ileum, rest of cecum, and peritoneum to such an extent that attempt at resection would spread the infection and increase the

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morbidity. (5) Exteriorization of the mass in a Mikulicz's type of procedure has been recommended when the cecal wall is gangrenous to such an extent that to return the cecum to the abdominal cavity would be unthinkable. At a later date, the ileo-colostomy would then have to be closed. An alternate procedure, recommended by Frehling,⁹ is to simply exteriorize the portion of the cecal wall which is gangrenous, form a cecostomy and allow the gangrenous portion of the cecum to slough; this results in a subsequent fistula, which may close itself or require minimal operative procedure at a later date. (6) Resection of the cecum may be necessary in cases where the cecum alone is involved and the terminal ileum and ascending colon appear to be in fairly good condition. If the blood supply to neither is jeopardized, the cecum itself may be resected and a side-to-end anastomosis be done between the terminal ileum and ascending colon just above the cecal region. (7) Schung²² advises conservative treatment with chemotherapy without resection if the clinical diagnosis can be made, on the rationale that the majority of the lesions would drain into the bowel and subside spontaneously. This is not recommended for a routine procedure.

CONCLUSION

Acute diverticulitis of the cecum is not as rare a disease as was previously believed, as evidenced by a total of now more than 100 cases in the literature. It must always be considered in patients exhibiting right lower quadrant pain and in whom a preoperative diagnosis of appendicitis is made. There is close resemblance to appendicitis in its pathology and action in the abdomen, which makes surgery the treatment of choice in this disease in all cases. Usually at operation for appendicitis, when a non-involved appendix is found, the possibility of cecal diverticulum, as well as a Meckel's diverticulum, must be considered. The operative procedures which have been recommended are given. The differential diagnosis, preoperatively, between acute appendicitis and diverticulitis of the cecum cannot be made. At operation, the differential diagnosis between the much more frequent carcinoma of the cecum, and diverticulitis of the cecum is very difficult to make. A careful evaluation must be made by the surgeon to avoid either a too radical resection for a minimal disease or a too limited resection in the case of a carcinoma, which merits the widest type of excision. Differentiation of this condition from a fibrosing type of tuberculosis of the cecum, from actinomycosis of the cecum and appendiceal abscess requires knowledge, experience and skill. Great care should be exercised in an attempt to carry out the correct procedure in each case. The condition may be present at any age in either sex, in fairly equal numbers, and if properly treated the mortality rate is low. The complications and sequelae are listed above. The one case reported here in which a hematoma of the abdominal wall resulted postoperatively is not a true sequela of the disease since there was no evidence of infection and it was obviously an error in hemostasis at time of operation.

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THE USE OF FULL THICKNESS SKIN GRAFTS IN THE REPAIR OF LARGE HERNIAE*

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THE PROBLEM OF REPAIR of the abdominal wall in patients with large hernial defects has taxed the ingenuity of the surgeon for many years. The procedures described attest by their number and diversity to the fact that no single satisfactory method has yet been found. It is the author's opinion that the use of full thickness skin as a buried graft in the repair of large herniae may be the answer to what has been, in some cases, an almost insoluble problem.

Skin, minus the epidermal layer, is known as cutis. Loewe¹ and Rehn² first advised using cutis in the repair of postoperative abdominal herniae. Cutis has been used extensively and almost exclusively in the United States by Cannaday.³ Cutis is elastic and contains a rich network of connective tissue fibres. When it is stretched and sutured under tension as a buried graft it soon undergoes metaplasia into firm connective tissue. Biopsies taken four years after cutis had been buried in deep tissues showed histological evidence of normal connective tissue, with no sign of retention cysts, hair follicles or sebaceous glands (Uihlein⁴). These findings have been confirmed by Peer and Paddock⁵ who, after scraping the epidermis, buried free skin grafts in the chest walls of human subjects. The grafts were removed for study at periods ranging from seven days to 12 months. They found marked connective tissue response at the site of implantation. Sweat glands were replaced by fibrous tissue and sebaceous glands had disappeared. Mair⁶ operated upon a man three months after he had used a full thickness skin graft in the repair of an inguinal hernia and noted that it was difficult to tell where the graft began since metaplasia into connective tissue was so profound. Histologic examination of the tissue showed highly vascular connective tissue with no identifiable dermal or epidermal elements. The graft was richly infiltrated with collagen and elastic fibres and was firmly adherent to the underlying muscle. No macroscopic or microscopic cysts or hair follicle remnants were seen. A few giant cells were present.

The findings of Mair and of Peer and Paddock indicate that full thickness skin is as efficacious as cutis and that the danger of inclusion cysts forming in the buried graft is negligible. Do wounds in which skin has been buried show an increased liability to infection? Harkins,⁷ in listing his objections to the use of cutis, named infection from organisms in the hair follicles and sudoriferous glands. However, Mair⁸ in 1945 reported only two cases of mild sepsis in 137 hernial repairs in which he had used whole skin grafts. In 1946 the same author⁹ stated that the incidence of wound sepsis and hematoma was no greater with this method than in any of the standard types of repair.

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Is whole skin preferable to cutis if one adopts the use of skin as a method of hernia repair? Whole skin is easier to obtain than cutis; operating time is consequently shortened. If removal of the epidermal layers of the skin is not necessary to prevent infection or the formation of inclusion and retention cysts there is apparently no reason for not using whole skin instead of cutis.

Harkins⁷ has said that in his opinion the bridging of defects in incisional or ventral herniae is seldom necessary and that he "has never seen a ventral or incisional hernia where the fascial layers could not be brought together." However, two of the author's small series of cases were incisional herniae secondary to shell fragment wounds of the abdomen, in which there had been such extensive loss of tissue in the abdominal wall that it was impossible to approximate peritoneum or fascia. It is true, of course, that such large defects are seldom seen in civilian surgery, but we believe that some of the recurrences seen after the repair of ventral and incisional herniae are probably due to the cutting through of sutures tied under tension in an effort to approximate fascial gaps. We prefer in such cases to use whole skin to bridge the fascial gap. We also believe that skin should be used to reinforce the repair in large herniae even when fascia can be mobilized.

CASE REPORTS

Case 1.—J. H. Age 28, male. Large hernia in left upper abdominal quadrant following laparotomy for shell fragment wound of abdomen. At operation in January, 1946, a defect in the peritoneum and fascia measuring 3 by 5 inches was found. The fascia could not be approximated. A full thickness skin graft was used to cover the defect. Postoperative course was uneventful. The patient was seen in July, 1948, at which time the repair was intact and the patient asymptomatic.

Case 2.—F. E. Age 24, male. Left upper abdominal hernia following laparotomy for shell fragment wound of abdomen. At operation in March, 1945, a defect in the fascia was found, measuring 4 by 3 inches. The fascia could not be approximated. Full thickness skin graft repair was done. Un eventful postoperative course. A letter received from the patient in Aug., 1948, stated that he was well and had no evidence of recurrence.

Case 3.—H. F. Age 45, male. Incisional hernia in right upper abdominal quadrant. At operation in May, 1946, a fascial defect was found measuring 3 by 5 inches. Partial fascial approximation was done with a full thickness skin graft to complete the repair and reinforce the fascia. Patient was seen in August, 1948, with no evidence of recurrence.

Case 4.—H. K. Age 51, male. An extremely obese man with a large incisional hernia in the right upper abdominal quadrant, of 18 years duration. At operation in September, 1946, a fascial defect measuring 4 by 4 inches was found. The fascia around the margins of the ring was extremely thin and frayed out. The fascia was approximated and a full thickness graft used to cover the area. This patient developed a large collection of serum in the wound which became grossly infected, necessitating incision and drainage. The repair remained firm and when seen in August, 1948, there was no evidence of recurrence.

Case 5.—M. P. Age 26, male. This patient had a large, recurrent direct inguinal hernia. At operation in September, 1946, there was a very large direct hernia with complete deficiency of the transversalis fascia. Repair was effected by suture of a flap of rectus sheath to Cooper's ligament, supplemented by a free full thickness skin graft behind the cord. Patient was seen in July, 1948, with no evidence of recurrence.

FULL THICKNESS SKIN GRAFTS

Case 6.—W. L. Age 53, male. Entered hospital for treatment of a bleeding duodenal ulcer and repair of a large incisional hernia in the right upper abdominal quadrant. In September, 1946, an infra-diaphragmatic vagotomy was done and the hernia repaired by approximation of the fascia and a full thickness skin graft. Postoperatively the patient developed massive pulmonary atelectasis and marked pylorospasm with prolonged gastric retention. In spite of intensive therapy including administration of urethane betamethylcholine hydrochloride and posterior gastroenterostomy the patient went steadily downhill and died in December, 1946. The hernia repair remained firm throughout and was intact at postmortem examination.

Case 7.—J. P. Age 71, male. Patient had a huge direct inguinal hernia. He was transferred to the surgical service after a perineal prostatectomy and operated upon in September, 1947. At operation a very large direct hernia was found, with complete deficiency of the transversalis fascia. A flap of rectus sheath was sutured to Cooper's ligament and a full thickness skin graft placed behind the cord. The patient was discharged in 9 days with a firm repair. The patient was seen in Aug., 1948, and had no evidence of recurrence.

SUMMARY

A review of the use of full thickness skin grafts in the repair of large hernial defects has been presented. A small series of cases has been cited, largely in an attempt to stimulate interest in a method which has not been used extensively in this country and which the author believes has great merit. By using skin, both as the sole tissue in repair, or as a supplement to inadequate fascial closure, difficult plastic procedures may often be avoided. This is especially desirable when the contemplated method of repair involves shifting or free grafting of large flaps of fascia with subsequent secondary fascial defects. The procedures used are simpler and less time consuming than the usual plastic fascial repairs. Whole skin grafts proved efficacious in several cases in this series which would have been extremely difficult to repair by any other method.

CONCLUSIONS

1. Whole skin, sutured under tension as a buried graft, is an effective substitute for fascia in the repair of large herniae.
2. There is little or no danger of the development of inclusion or retention cysts in these grafts.
3. There is usually enough redundant skin over the hernia to provide for the graft. The need for a secondary donor site seldom arises.
4. The incidence of infection and hematoma formation is no greater than in other types of repair.
5. This method can be used to correct some large herniae which would be very difficult to repair by any other type of procedure.

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CIRSOID ANEURYSM OF THE SCALP: REPORT OF A CASE*

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CIRSOID ANEURYSMS are discussed in the literature under various titles. Virchow believed them to be tumors of blood vessels and called them *racemose* aneurysms. Dupuytren considered them to be arterial varices, while according to Virchow, it was Breschet who suggested the term *cirsoid* from the Greek *kirnos* meaning varix. They are known also as arterial angiomas or aneurysms by anastomosis. Reid in 1925 published an account of 33 cases of arterio-venous communications, including four cirsoid aneurysms. He made no distinction between the various types and used the term arteriovenous aneurysms to designate all conditions where abnormal communications between arteries and veins existed.

Cirsoid aneurysms of the scalp are rare. In other parts of the body, the trauma leading to this lesion is most often a penetrating wound. In the region of the skull, both intracranially and extracranially, the injury is usually a non-penetrating one. A distinctive feature of cirsoid aneurysms of the scalp is their progressive nature in contrast to the tendency toward stabilization often shown by similar lesions elsewhere in the body.

It is now generally agreed that the cirsoid aneurysm is a form of arterio-venous fistula in which the earliest abnormal communications are between the arterioles and the venules. The inciting factor is believed to be trauma, frequently trivial, which results in rupture of the small vessels and brings about false communications between the smaller arteries and veins. The ultimate effect of such abnormal openings is to divert blood under arterial pressure directly into the venous system with resultant venous dilatation. The decreased resistance to the flow of blood from artery to vein at the site of the fistula as compared to the resistance to the flow of blood through the capillary bed elsewhere leads to an increase in the volume of blood flowing through the fistula and results in dilatation of all the vessels in the neighborhood. The cirsoid aneurysm comes to be composed essentially of two parts, the fistula itself and the dilated afferent and efferent vessels.

There is a growing tendency in modern literature to disregard the term cirsoid aneurysm and to discuss these lesions with other types of arteriovenous fistulas. However, the term *cirsoid* is so deeply entrenched in medical literature that its continued use seems justified. Certainly the term has come to convey the clinical picture now familiar to all. One need only recall that it is a type of arteriovenous aneurysm.

A patient with a cirsoid aneurysm of the scalp has recently been success-

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fully treated at the University of California Hospital. The case history and a brief discussion of the problem follow.

ARTERIOVENOUS ANEURYSM OF THE SCALP

F. P., a 35-year-old white male, sustained a blow on the head resulting in a scalp laceration in an auto accident in February, 1942, 5 years before entering the University of California Hospital. The wound was immediately sutured and the patient had no further distress until 2½ years later when he first noted swelling in the region of the previous injury. The mass steadily increased in size and the right temporal artery became

visibly enlarged and tortuous. For 2 months prior to admission he was aware of a "swishing" noise when reclining, more noticeable when the head was turned to the right side. He had noted that the noise was synchronous with his pulse.

At the time of entry there was a diffuse swelling which occupied the right fronto-parietal region of the scalp (Fig. 1). This mass was composed of tortuous vascular channels extending posteriorly to the level of the external auditory meatus. The overlying skin was reddened, scarred and somewhat thinned out. The lesion was everywhere soft, compressible and non-tender. A continuous murmur with systolic accentuation was heard over it and a thrill could be palpated over its midportion. Both temporal vessels were dilated and tortuous. Compression of one or both of the temporal arteries decreased the size of the mass but did not obliterate it, nor was the bruit completely stilled. The optic fundi were normal and the auditory acuity was bilaterally equal. The remainder of the physical examination was not remarkable. There



FIG. 1.—The preoperative photograph demonstrates the diffuse nature of the aneurysm.

was no tachycardia and the heart was of normal size and shape. The pulse was not slowed by compression of the aneurysm.

In order to obtain arteriograms, the right common carotid artery, along with its internal and external divisions, was exposed under local anesthesia through an incision parallel to the anterior border of the sternomastoid muscle. While the internal carotid artery was temporarily occluded by a bull-dog clamp, 15 cc. of 20 per cent thorotrust solution were injected into the external carotid artery. Thereafter, an injection of 25 cc. of thorotrust solution was made into the internal carotid artery while the external division was occluded (Fig. 2). A series of roentgen films was taken after each injection.

The intracranial circulation from the internal carotid artery appeared to be essentially normal. However, there was a channel, probably taking origin from the ophthalmic artery, which traversed the supraorbital region beneath the roof of the orbit and filled a vessel lying within the scalp (Fig. 3A). The injection of the external carotid artery showed two large and tortuous arteries, one in the frontal and one in the parietal region (Fig. 3B). The second film of the series showed filling of widely dilated tortuous channels which were presumably veins. The angioma received its main blood supply from the external carotid artery, although some of its supply came from the internal carotid artery through vessels which traversed the orbit just below the orbital roof.

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Operation was performed under intratracheal nitrous oxide anesthesia. Bilateral incisions exposed greatly enlarged and tortuous temporal arteries along with their accompanying veins. Each temporal artery was divided and ligated (Fig. 4, insert). A semi-circular fronto-parietal scalp incision was then made extending through the galea aponeurotica, and the entire scalp flap was reflected forward. The individual vessels were visualized and a large mass of tortuous, dilated and engorged arteries and veins was

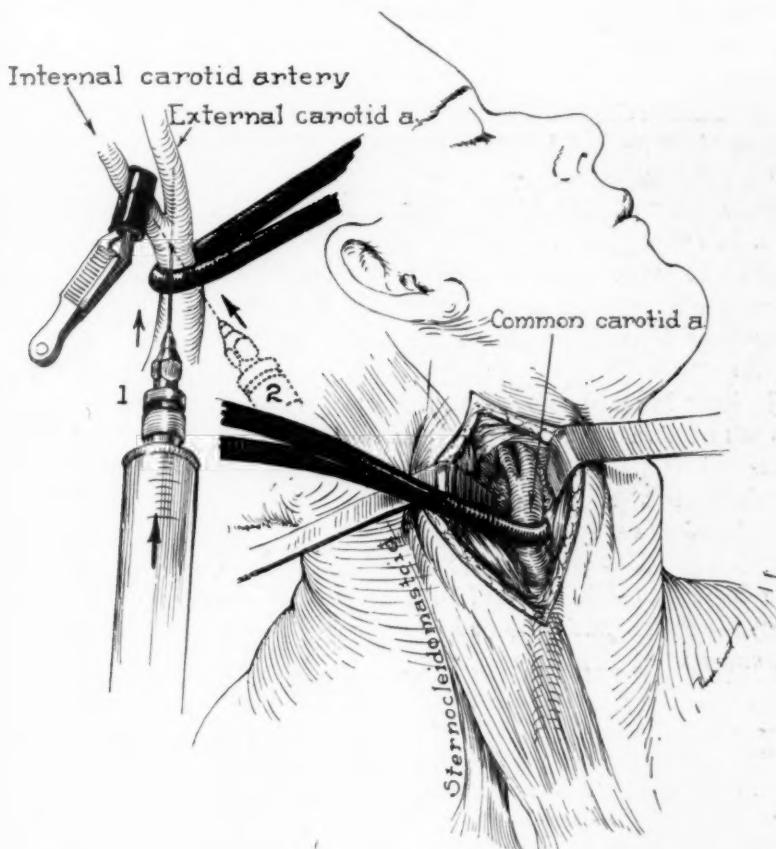


FIG. 2.—Angiograms of the aneurysm and its associated vasculature were obtained by injecting thorotrust into the external and internal carotid arteries.

completely removed (Fig. 4). The flap was replaced, sutured and held adherent to the skull by a firm pressure dressing.

The patient's postoperative course was uneventful and the wound healed *per primam*. There was no evidence of a bruit or thrill, and the patient was no longer conscious of the subjective noise noted before operation. All dilated and tortuous channels had apparently been removed (Fig. 5).

DISCUSSION

Cirsoid aneurysms are most frequently traumatic, though sometimes they appear to arise independently through the presence of a pre-existing congenital

vascular abnormality of an angiomatic nature. They are considered to occur secondary to a congenital arterial angioma, or more rarely to a venous angioma. Although trauma is usually considered to be the inciting cause, some authors believe that inflammation plays a prominent role in their production.

Sites of predilection are the scalp, face, hands, and feet. Actually they may develop anywhere in the body, although there are few reports in the literature indicating the presence of cirsoid aneurysms associated with the viscera. One such report concerns a cirsoid aneurysm of the left gastric artery secondarily producing peptic erosion and copious gastric hemorrhage.



FIG. 3.(A)—Roentgen film taken immediately after arterial injection; demonstrates the arterial supply of the aneurysm.

Clinically the aneurysm is easily diagnosed. It is a painless lesion even to firm palpation but causes distress because of the beating sensation of which the patient is constantly aware. Frequently intense headache and tinnitus may be experienced. Beneath the bluish tinged skin, the cirsoid aneurysm appears as an irregular, diffuse, elevated mass which is not only soft but easily compressible. When pressure is released the mass quickly fills with blood and returns to its former size. There are usually visible pulsations, and a thrill synchronous with the arterial beat can be palpated. A blowing murmur can be

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heard on auscultation over the aneurysm. This murmur may be continuous, continuous with systolic reinforcement, or biphasic with a strong systolic and a weaker diastolic component, or with simply a systolic one. Compression of the tumor causes disappearance of the murmur and thrill. The impression imparted to the examining hand is that of a mass of worms.

It is most important to determine the presence of communications with enlarged vessels within the skull. The injection of radiopaque material into



FIG. 3.(B)—Roentgen film taken immediately after arterial injection; demonstrates the arterial supply of the aneurysm.

the afferent arteries followed by an appropriate series of roentgen films will, in most instances, demonstrate the extent of the involvement.

The cirsoid aneurysm is to be differentiated from an arteriovenous aneurysm and an angioma. The arteriovenous aneurysm affects the larger vessels and has but a single communicating fistula, pressure upon which causes the bruit or thrill to disappear. This phenomenon has been mentioned as Terrier's sign. In cirsoid aneurysms, the communications are multiple, are between the smaller vessels, and the bruit or thrill disappears only when pressure is exerted

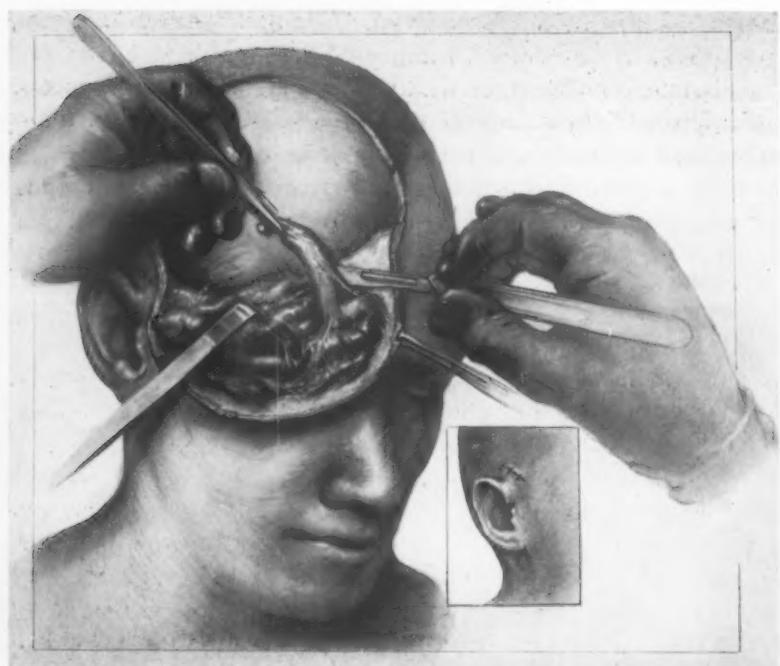


FIG. 4.—Diagrammatic representation of the operative procedure. Complete excision of the aneurysm was performed after preliminary ligation of both temporal arteries.



FIG. 5.—Two weeks after operation the wound had completely healed (A). The components of the aneurysm had been totally eradicated and the patient was no longer aware of the subjective "swishing noise" that he had noted before operation. The appearance of the operative area six months after surgery is shown in B.

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over the entire surface of the tumor. Congenital angiomas appear as simple red or bluish areas over which there is no thrill, bruit or pulsation.

Most authors agree that cirsoid aneurysms never heal spontaneously. Various methods of treatment have been proposed. Among these are application of various caustic agents, injection of sclerosing solutions, compression, ligation of the afferent vessels, electrocoagulation, radiation and extirpation. Patey has recently described the successful use of arterial ligation combined with venous injection. The inefficiency of proximal arterial ligation as the sole means of treatment is well recognized. However, the value of preliminary ligation of the principal afferent artery or arteries at a point proximal to the lesion cannot be denied.

The most effective means of treatment is by complete surgical removal. In spite of all precautions this operation carries some risk from severe hemorrhage. Cirsoid aneurysms are cured by excising or eliminating by ligation the abnormal communications between arteries and veins. It is not always possible to ascertain the exact site of such fistulae. In order to be certain that all of them have been extirpated, it is frequently necessary to remove large masses of dilated vessels. If an abnormal opening is overlooked, some of the dilated vessels will persist. This phenomenon has led some observers to regard cirsoid aneurysms as neoplastic in origin. However, the evidence, both histologic and from follow-up studies, suggests that they are not neoplastic.

SUMMARY

Cirsoid aneurysms of the scalp are usually progressive in nature and result most frequently from non-penetrating trauma to an area containing a pre-existing vascular lesion of a congenital angiomatic nature. The cirsoid is a form of arteriovenous aneurysm exhibiting multiple abnormal communications between the smaller arteries and veins. The decreased resistance of blood flow through the multiple communications leads to a large volume flow of blood to the area resulting in a dilatation of all the vessels in the neighborhood of the fistula. The enlarged vessels are clearly visible and resemble a mass of worms beneath a thinned out and bluish tinted scalp. In contrast to the more common congenital angioma, the cirsoid aneurysm pulsates and exhibits a bruit and thrill over the abnormal communications.

Although many methods of treatment have been advocated, the procedure of choice is complete extirpation accompanied or preceded by ligation of the afferent arteries.

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PRIMARY SPLENIC NEUTROPENIA: A SPECIFIC INDICATION FOR SPLENECTOMY*†

REPORT OF A CASE

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UNTIL RECENTLY, the conditions or diseases considered as an absolute indication for splenectomy were limited to traumatic rupture, idiopathic thrombocytopenic purpura, primary splenic anemia, and congenital hemolytic jaundice. In the past several years many diseases and entities have been added to this list. Recently included is a disease now known as primary splenic neutropenia.

Felty¹ was possibly the first to describe a condition or syndrome which was primarily a neutropenia, without any specific etiology, but which was associated with symptoms and findings of arthritis, skin manifestation, and splenomegaly. In 1924 he described and reported five cases. The condition was then named Felty's syndrome.

In 1932 Hanrahan and Miller² performed a splenectomy in a case of Felty's syndrome with complete alteration of the arthritis and return of the white blood count to normal. In the same year, Turley¹¹ suggested that the spleen destroyed polymorphonuclear leukocytes.

In 1939 Wiseman and Doan¹² reported three cases of leukolysis resulting in a specific granulopenic syndrome which they believed was due to splenic dysfunction and were cured by splenectomy. In 1942, when the same two authors¹³ reported five additional cases, the name primary splenic neutropenia was used to describe the syndrome or disease. At this time they reported what was believed to be a hitherto unrecognized cause of neutropenia, resulting from a pathologically altered, physiologic function of the spleen.

It is generally accepted at the present time that the spleen has three definite functions in the adult: (1) destruction of red blood cells, (2) production of lymphocytes, and (3) the storage of blood. Several authorities think the spleen performs other functions but these have not been definitely established.

The spleen may develop a selective destructive function of certain elements in the peripheral circulating blood, resulting in idiopathic thrombocytopenic purpura, if the platelets are destroyed; in hemolytic jaundice, if the erythrocytes are selected for destruction; and primary splenic neutropenia, if the leukocytes are the victims.

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Since the original descriptions of this unusual syndrome or disease characterized by a granulocytopenia, splenomegaly, and the ability of the bone marrow to function normally or show evidence of panhyperplasia, very few cases have been reported in the literature.^{3, 4, 5, 6, 7, 12, 13}

CASE REPORT

W. G. M., a white male, 50 years of age, admitted to the Medical Service March 22, 1944, at which time his chief complaints were: Protruding bleeding hemorrhoids, fleeting joint pains, and occipital headaches. The joint pains began about one year before admission and shifted from one joint to another. At this admission his knee joints were causing some distress. The physical examination was negative except for protruding hemorrhoids and a scaly dermatitis of both legs which has been present for many years. Laboratory findings were negative. The patient did not have a blood count during this period of hospitalization. A hemorrhoidectomy was performed and was uneventful. The patient was discharged June 28, 1944.

He was readmitted to the Medical Service on Sept. 19, 1945, with complaints of pain in both shoulder joints, knee joint, and pain in the feet. He also complained of feeling below par, tired easily and became tremulous, nervous, and dizzy on slight exertion. The physical examination was essentially negative except for limitation of abduction of the arms to one-half of the normal range. A hyperkeratotic dermatitis was noted on both tibial areas of the legs.

On November 30, 1945, examination revealed the spleen to be palpable, three inches below the left costal arch. There was a small lymph node in the submental region and an inguinal node, 2 cm. in size, on the right side.

The patient during this period of hospitalization ran a remittent and intermittent low grade fever, never above 100° F. Roentgenograms of the spine revealed a mild hypertrophic lumbosacral arthritis. The most conspicuous findings were the changes in the white blood counts (Table I). On September 28, 1945, hemoglobin, 95 per cent; ery-

TABLE I.—Circulating Blood Picture—During Second Hospitalization

Date	Erythrocytes	Hemoglobin	Leukocytes	Neutrophils
9-26-45	5,150,000	13.8 Gm.	1,900	59
10-9-45	4,600,000	13 Gm.	2,100	32
10-12-45	5,050,000	13.8 Gm.	1,700	20
10-22-45	4,700,000	13 Gm.	2,400	31
12-20-45	14 Gm.	1,500	16
1-24-46	4,610,000	12.5 Gm.	2,900	21
2-6-46	2,200	54
3-26-46	3,950,000	9.5 Gm.	900	..
4-24-46	3,300,000	10 Gm.	1,700	..
6-20-46	4,000,000	2,200	..

throcytes, 5.15 M, with total leukocytes of 1,900; polys, 59 per cent; lymphocytes, 37 per cent; eosinophiles, 3 per cent; sedimentation rate, 5 mm. Sternal marrow biopsy was done and this revealed many mature erythrocytes, a rare nucleated cell and myeloblasts, 4; premeloblasts, 26; myelocytes, 8; band forms, 16; segmental neutrophils, 2; macroblasts, 44. The icterus index was normal. On November 30, 1945, a diagnosis was made of lymphatic leukemia in aleukemic phase. On the same date the patient was seen by the consultant in dermatology who made a diagnosis of lichen planus, lichen simplex, chronicus or possible Boeck's sarcoid of the skin lesions of the legs.

A biopsy of skin was performed and on January 29, 1946, a diagnosis of lichen simplex was made.

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The patient was treated by penicillin and pentnucleotides and was discharged from the Medical Service June 25, 1946.

He was readmitted to the Medical Service on July 24, 1946, with the chief complaint of a painful, swollen area, anterior surface of left thigh. The area had been present for several days. Physical examination disclosed a swollen, reddened, tender area of left thigh, enlarged spleen, and palpable liver. The abscess of the thigh was incised, drained, and healed under penicillin therapy. The blood picture continued to show a normal erythrocyte count and hemoglobin value, and a leukopenia with low neutrophil count (Table II). Sternal punctures were performed and showed a normal sternal marrow with

TABLE II.—Circulating Blood Picture—During Third Hospitalization

Date	Erythrocytes	Hemoglobin	Leukocytes	Neutrophils	Platelets
8-28-46	4,830,000	12 Gm.	1,900	32	385,000
9-10-46	4,790,000	12.5 Gm.	1,800
10-7-46	5,250,000	14.0 Gm.	2,500	62
*12-3-46	5,400,000	12.5 Gm.	14,400	94
12-9-46	5,020,000	13.5 Gm.	18,100	88
12-16-46	4,710,000	12 Gm.	13,100	72
12-24-46	4,880,000	13.5 Gm.	9,400	64	800,000
1-28-47	5,360,000	14.5 Gm.	10,800	41	400,000

* Day following splenectomy.

the ability of the marrow to form normal erythrocytes and leukocytes (Table III). The biopsy of the local inguinal lymph node showed fibrosis and no evidence of leukemia. On November 5, 1946, patient was seen by a consultant in medicine and hematology who stated that the patient had had a persistent leukopenia but has developed no anemia. Bone marrow examinations indicated that neutrophils were being formed properly so that their reduction in the peripheral blood must have been from too rapid destruction. The spleen was enlarged and obviously pathologic, and it was logical to assume that this was the site of excessive destruction. Leukemia was not probable because there was no anemia and it was not suggested in the bone marrow. He suggested biopsy of a lymph node to finally exclude lymphocytic leukemia. If this was excluded by the biopsy, he advised splenectomy.

TABLE III.—Sternal Puncture—Bone Marrow Studies

	8-26-46	10-9-46
Segmented neutrophil.....	25	Bands..... 41
Band neutrophil.....	22	Metamyelocytes pmm..... 12
Metamyelocyte neutrophil.....	14	Myelocyte, pmm..... 21
Metamyelocyte eosinophilic.....	1	Myelocyte, eosinophil..... 7
Myelocyte.....	4	Premyelocytes..... 3
Promyelocyte.....	3	Blast cells..... 6
Blast cells.....	5	Lymphocytes..... 10
Lymphocytes.....	4	
Megaloblasts.....	5	Total..... 100
Normoblasts.....	11	
Monocytes.....	1	
Unclassified.....	5	
Total.....	100	

The patient was seen in consultation by the Surgical Service on November 25, 1946, at which time the spleen was greatly enlarged and extended below the level of the umbilicus. The liver was not palpable and there was no evidence of ascites or anemia. The lymph node revealed fibrosis and the sternal marrow exhibited no abnormalities. A splenectomy was recommended and was accomplished on December 2, 1946, at which time the spleen was found to be greatly enlarged, occupying the entire left upper quadrant. The spleen was lobulated and the lower pole extended below the limit of the umbilicus. The spleen was so large and boggy that it was impossible to deliver it through the wound prior to isolating and dividing the splenic pedicle. There was, also, a small accessory

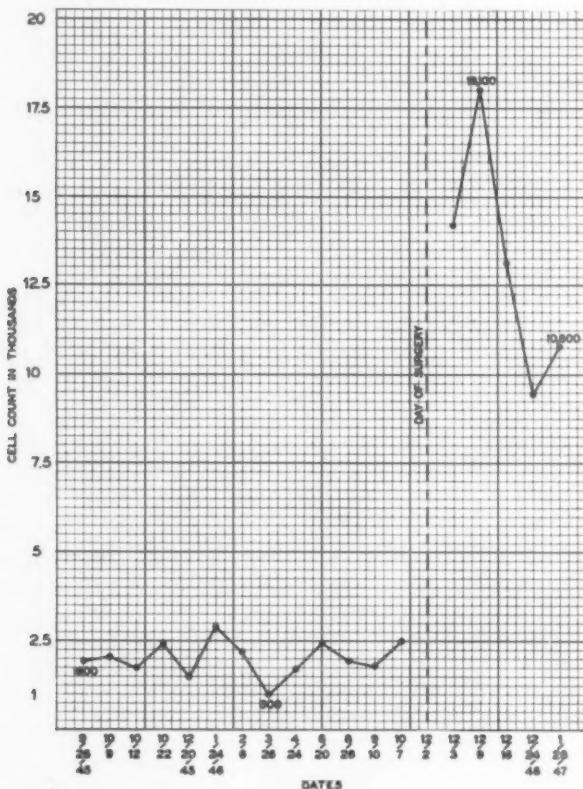


CHART I

White blood count prior to and following splenectomy.

spleen which measured 1 cm. in diameter; it was found near the hilus of the spleen. The liver was normal in size, color, and shape and its margins were smooth and sharp. There was no evidence of ascites or portal obstruction.

Prior to surgery the erythrocyte count and hemoglobin value were normal and the leukocytes revealed a persistent leukopenia varying from 1,400-2,500 (Table II).

The day following surgery the leukocyte count was elevated to 14,400 with 94 per cent polys and remained elevated during the remainder of the patient's stay in the hospital. (Table III and Chart I.)

The pathologist reported the specimen consisted of a spleen which was greatly enlarged and had a bluish discoloration. The discoloration was more marked in some areas where the capsule had been raised by hemorrhage. On the superior lateral aspect

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of the spleen numerous small yellow plaques were impacted in the capsule, the average diameter being approximately 3 mm. One large plaque was found to measure approximately 1 cm. in diameter. The specimen was very soft and the capsule was wrinkled. On cut section it was blood-red in color. There was considerable oozing of blood from the cut surfaces. The cut surface presented a speckled appearance, the specks being uniformly distributed and approximately 0.5 mm. in diameter and of a bluish-white color.

A second specimen consisted of an accessory spleen, (1 cm. in size).

Microscopic Examination. The capsular surface was irregular but smooth. There was one nodule of symmetrically arranged fibrous tissue which revealed partial hyalinization. One area of subcapsular hemorrhage exhibited no hemolysis or organization and was apparently traumatic.

There was moderate dilatation of sinuses and mild reticulo-endothelial hyperplasia. Trabeculae were sharply defined and there was no fibrosis. Follicles were prominent and normal architecture was preserved. Arterioles revealed mild sclerosis. There was a small amount of pigment present which was not abnormal in amount. Sinusoids contained many mono- and multinucleated giant cells with oval nuclei and buff cytoplasm. Some contained small vacuoles and some contained nuclei of polymorphonuclear leukocytes.

The picture here presented was not typical of splenic anemia or Banti's syndrome, and it revealed no evidence of malignancy. It was compatible with the disease described as primary splenic neutropenia.

The patient made an uneventful recovery following surgery and was transferred back to the Medical Service on December 19, 1946, for further observation and follow up. The patient was discharged from the hospital on February 5, 1947, completely relieved of all symptoms, blood picture normal, and skin lesions completely healed.

CONCLUSIONS

1. A case of primary splenic neutropenia was presented as clinically cured by splenectomy and removal of an accessory spleen.
2. The case presented conforms to the description made by Wiseman and Doan in 1939 and 1942. The condition resembled Banti's Syndrome, Felty's Syndrome, subleukemic myeloid leukemia, hyperplastic anemia, malignant neutropenia, or certain types of chronic infection.
3. The disease results from a splenic dysfunction as a result of selective destructive action of the reticulo-endothelial cells of the spleen closely related to congenital hemolytic icterus and essential thrombocytopenic purpura in which cases the erythrocytes and platelets are destroyed respectively.
4. A definite and accurate diagnosis was dependent upon a complete clinical survey of the patient and a detailed study of sternal marrow, circulating blood, and biopsy of a lymph node.
5. This disease should be included in the long list of diseases in which splenectomy is definitely indicated.

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UNUSUAL METASTATIC MANIFESTATIONS OF BREAST CARCINOMA*

III. METASTATIC INVOLVEMENT OF PREAURICULAR LYMPH NODES AND PAROTID GLAND. A REPORT OF FIVE CASES

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ONE OF THE EARLIEST SITES for the appearance of metastatic mammary carcinoma is the ipsilateral axillary lymph nodes. Occasionally axillary node metastasis is discovered before the primary breast lesion is demonstrable.** Martin and Morfit¹ found cervical node metastasis to be the first sign of breast carcinoma in 0.3 per cent of the breast cases reviewed by them. As the disease progresses the supraclavicular nodes may become invaded; the node situated behind the head of the clavicle in the sternocleidomastoid clavicular angle is usually the first to become involved. This phenomenon is comparable to the appearance of the so-called sentinel node in advanced carcinoma of the stomach. The posterior cervical chain of nodes ultimately may become cancerous and in advanced cases of breast cancer node involvement may extend as high as the mastoid or occipital prominence.

It is however unusual for the preauricular lymph nodes or parotid gland to become invaded by the disease. The preauricular lymph nodes may be divided into three groups. (1) A superficial or suprafascial group which consists of one or two, occasionally three or four nodes situated in the neighborhood of the tragus. They are found in approximately one out of three individuals. (2) A subfascial group, containing one or two and occasionally three or four nodes, which lies between the fascia and the superficial surface of the parotid gland. These nodes are present in most individuals. (3) A deep intraglandular group composed of four to ten nodes situated in the areolar tissue which unites the superficial with the deep lobes of the parotid. These nodes are constantly present.

Three patients in whom the preauricular nodes and two in whom the parotid gland became involved secondary to carcinoma of the breast are reported in this communication.

Case 1.—A. W., a 37-year-old white woman underwent a left radical mastectomy in January, 1940, at the Memorial Hospital. The pathologic finding was an infiltrating duct carcinoma grade 3 metastatic to multiple axillary lymph nodes. The patient received postoperative roentgenotherapy to the left axilla and remained apparently free of disease for more than three years. A painful swelling then appeared over the upper left chest

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near the sternal margin and a tiny node became palpable behind the head of the left clavicle. These were interpreted as metastatic disease and regressed with roentgenotherapy.

The patient remained asymptomatic for about seven months and then developed cough and dyspnea. Roentgenographic studies made of the chest at this time revealed evidence of pulmonary metastasis. On examination a firm, smooth, freely movable, painless subcutaneous nodule about one cm. in diameter was palpated in the left preauricular region and was interpreted as metastatic involvement of a preauricular lymph node. An aspiration biopsy of this node was reported as carcinoma. No other nodes were palpable in the supraclavicular or cervical regions. The involved node in this case was one of the suprafascial group. The patient succumbed to the disease three months after the appearance of the preauricular node enlargement.

Case 2.—A. F., a 48-year-old white woman underwent a right radical mastectomy in 1940 at the Memorial Hospital. Pathologic examination revealed an infiltrating duct carcinoma grade 3 metastatic to one axillary node.

The patient remained apparently free of disease for about four years and then developed a bony prominence in the left parietal region of the skull with pain in the lumbar spine. Roentgen studies made at this time revealed evidence of metastasis to the ribs, lumbar spine, pelvis and skull. Radiation therapy was administered to the lumbar spine and pelvis with amelioration of the pain.

About six months later pain developed in the dorsal spine. Roentgenographic investigation revealed metastasis to the thoracic and lumbar spine with collapse of the body of the 6th dorsal vertebra. Several months later (about five years after her mastectomy) a smooth, firm, freely movable, non-tender, subcutaneous node about 1.0 cm. in diameter was found in the left preauricular region. This was interpreted clinically as metastatic disease in a preauricular lymph node of the suprafascial group. There was no other external evidence of disease and no palpable adenopathy. The patient died of the disease about one month after the appearance of the preauricular node.

Case 3.—L. A., a 46-year-old white woman underwent a right radical mastectomy at the Montefiore Hospital in January, 1947. The pathologic report was undifferentiated carcinoma involving the pectoral muscles and metastatic to the axillary fat and lymph nodes. Roentgenograms of the lumbar spine and pelvis made before operation revealed no evidence of metastasis.

The patient was readmitted to the Montefiore Hospital three months later because of massive recurrence in the right anterior and posterior chest wall, right arm and anterior abdominal wall. There was no supraclavicular, cervical or right axillary adenopathy. One firm 2 cm. node was palpable in the left axilla. The left breast was apparently normal. The liver was enlarged and nodular.

A subcutaneous nodule was noted in the right preauricular region about one month after admission. It was 2 cm. in diameter, smooth, movable and non-tender, evidently suprafascial in location. Aspiration biopsy was reported as carcinoma. The patient died about two weeks after the preauricular node was discovered.

Case 4.—J. V., a 68-year-old white woman came to the Memorial Hospital in December, 1943, because of a painless lump in the right cheek of three months' duration. According to the patient the swelling was as large as a pea when first noticed by her and increased rapidly in size.

Examination revealed a 3 cm. firm, well encapsulated mass in the right preauricular region which appeared to be embedded in the substance of the parotid gland (Fig. 1). No lesions were noted in the oral cavity, pharynx or larynx. There were no palpable supraclavicular or cervical nodes. The general physical examination revealed a hypertension

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of 200/90 but nothing else of note. A diagnosis of mixed tumor of the parotid and hypertensive heart disease was made.

An aspiration biopsy of the tumor mass was reported as either lymphosarcoma or anaplastic carcinoma with the evidence favoring the latter diagnosis. To establish a definite diagnosis an excisional biopsy was performed. Dr. Fred Stewart's report and comment was "Adenocarcinoma grade 3. This may not be a primary parotid tumor. Is there anything in the breast?" This report prompted a reexamination of the patient's breasts. The findings were as follows: The breasts were small, symmetrical and the nipples normal. There was a slight fullness in the right breast on palpation. One small node was felt in the right axilla. On elevating the right breast a dimple was apparent in the inframammary sulcus (Fig. 2). Palpation of this region disclosed a poorly defined, non-tender 3 cm. mass. Aspiration biopsy of this lesion was reported as carcinoma. Roentgenograms of the lungs were negative for metastasis.



FIG. 1



FIG. 2

FIG. 1. (Case 4)—The swelling in the parotid region is traversed by the scar of the biopsy incision.

FIG. 2. (Case 4)—The retracted area is produced by the underlying breast carcinoma.

The face and breast lesions underwent considerable regression with roentgenotherapy. The patient has remained asymptomatic and there has been no evidence of activity of the neoplasm up to the present time—a period of four and one-half years. It is not possible in this case to determine whether the metastasis was to the parotid or to the intraglandular group of preauricular nodes.

Case 5.—L. C., a 58-year-old white woman underwent a right radical mastectomy for advanced mammary carcinoma at another institution in September, 1943. She was asymptomatic for about three years and then developed pain in the cervical region, right arm and shoulder. Roentgenograms taken at this time revealed no abnormalities of the chest but there was destruction of the 6th cervical vertebra which was interpreted as metastasis. Despite roentgenotherapy pain in the right arm and shoulder continued and the patient gradually lost the function of this extremity.

In October, 1946, six weeks before admission to the Montefiore Hospital, a painless mass appeared suddenly in the right parotid region and increased rapidly in size. Exam-

ination on admission revealed a well-healed right radical mastectomy scar. There was paresis of the muscles of the right shoulder with motor and sensory loss in the right upper extremity probably due to involvement of the brachial plexus. A firm, non-tender, golf ball sized mass was found in the right parotid region (Fig. 3). It was fixed to the underlying structures but the overlying skin was movable. There was no intra-oral lesion and no secretion could be expressed from Stenson's duct. No axillary, supraclavicular, cervical or inguinal nodes were palpable. Abdominal palpation revealed the liver to be enlarged and nodular. Roentgenological studies disclosed metastases to the skull, ribs, 5th, 6th and 7th cervical vertebrae and an area of destruction in the right mandible (Fig. 4). A biopsy



FIG. 3



FIG. 4

FIG. 3. (Case 5)—This reveals the diffuse enlargement of the parotid gland.
FIG. 4. (Case 5)—A large defect involves the angle and ramus of the mandible.

of the parotid mass was reported as carcinoma. About one month after admission the patient became stuporous, probably from cerebral metastases, and she died shortly thereafter.

A postmortem examination revealed widespread metastatic mammary carcinoma. The right parotid gland appeared grossly to be extensively involved by grayish pink tumor tissue and histopathologic examination showed complete replacement of the gland by tumor. No parotid gland epithelium could be recognized. The angle of the right mandible was completely eroded, the defect in the cortex extending for 3 cm. up the ramus and for 1 cm. along the body of the mandible. Microscopic examination revealed necrotic tumor tissue replacing the marrow and invading the periosteum.

As in the preceding case it is impossible to determine whether the breast carcinoma metastasized primarily to the parotid or to the intraglandular preauricular nodes. Direct extension to the parotid from a mandibular metastasis is another possibility.

COMMENT

Each of our patients was in an advanced stage of the disease at the time that preauricular node or parotid gland involvement occurred and four of them died within a short time after invasion of these structures was observed. It

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would seem that preauricular node or parotid gland metastasis is a late manifestation of mammary cancer.

In two patients the involved preauricular node was on the same side as the breast lesion and in one patient (Case 2) it was on the contralateral side. Both patients with parotid gland metastasis had the involvement on the same side as the primary lesion of the breast. It is of interest that in no instance was there palpable evidence of supraclavicular or cervical adenopathy at the time the preauricular node or parotid gland became invaded except for one minute node behind the head of the clavicle in Case 1. The statement of Paget² in reference to bone metastasis that "some bones suffer more than others; the disease has its sites of election" may also apply to the sites of election of lymph node metastasis.

It has been shown in a previous communication³ that metastasis to the mandible from mammary carcinoma is an unusual occurrence. It is not possible to determine in Case 5 whether the mandible was involved by extension of the disease from the parotid gland or vice versa. It is possible that there was concurrent, independent involvement of mandible and gland.

Since the breast is one of the most frequent sites for the origin of cancer in women this organ should be suspected in instances of metastatic disease of obscure origin (Case 4). This case also illustrates the importance of elevating the breast and examining both visually and manually its under surface, a procedure which should be part of every routine breast examination.

SUMMARY AND CONCLUSIONS

1. Three cases of preauricular lymph node and two cases of parotid gland involvement by metastatic carcinoma of the breast are reported. Metastasis to these sites is of infrequent occurrence.
2. In one patient there was metastatic invasion of the mandible associated with parotid gland metastasis. In another patient the condition simulated a primary neoplasm of the parotid.
3. Preauricular node and parotid gland involvement are late metastatic manifestations of breast carcinoma.

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BRIDGING OF ESOPHAGEAL DEFECT BY PEDICLED FLAP OF LUNG TISSUE*

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GRAFTS OF LUNG TISSUE have been widely used for reinforcing sutures of the bronchial stump following lobectomy and pneumonectomy. In lobectomy, which as a rule is performed for benign lesions, preference is given to a pedicled flap. In pneumonectomy where the high level of bronchus dissection does not permit preservation of a pedicled flap, Churchill² was successful in securing the bronchial closure by a free graft of lung tissue taken from the periphery of the excised lung. The following case history will demonstrate that in surgery of the thoracic esophagus, lung tissue can be used for protecting critical areas in precisely the same way as omental grafts are used in abdominal surgery.

Case Report: A 56-year-old male patient was admitted to the Israel Zion Hospital with a brief history of esophageal obstruction. Roentgenographs (Fig. 1) revealed a half-moon shaped filling defect of the middle portion of the thoracic esophagus. Roentgenologic (Doctor Tolk) diagnosis was benign tumor, probably leiomyoma. Esophagoscopy (Doctor Silverstein) and biopsy revealed small ulcerations of the mucosa in the obstructed area. The impression of the endoscopist was also that of a submucous benign tumor.

At operation on June 20, 1947, the left thoracic cavity was entered through the bed of the 6th rib. A large tumor of the muscular sheath of the esophagus was found, extending from the inferior margin of the aortic arch to 2 inches below the level of the bifurcation. The tumor mass occupied the entire circumference of the esophagus. In order to expose and excise it, two segmental arteries arising from the descending aorta had to be severed. The muscle tube comprising the entire muscular wall of the esophagus was partly interwoven with and greatly thinned out by the tumor (Fig. 2). In order to insure radical removal, the entire muscular tube was removed with the neoplasm. Great care was taken not to pierce the mucosa, although at two points (apparently the areas from which the biopsy was taken) the remaining mucosal layer was extremely thin. After completion of the excision there remained a mucosal cylinder 10 cm. in length, deprived of its muscular sheath.

Since the vascular supply of this denuded area was probably insufficient because of the ligation of two segmental arteries and the scar formation in the mucosa, it was felt that the denuded area should be covered by viable tissue. Therefore, the adjacent upper segment of the lower lobe was mobilized and wrapped around this portion of the esophagus. A complete cover was thus obtained. The lung was fastened to the muscular sheath of the esophagus above and below the defect, in a manner demonstrated in the illustrations (Fig. 3). The phrenic nerve was crushed above the diaphragm, a rubber catheter inserted through a separate stab wound in the 9th intercostal space and the incision of the chest wall closed in layers. Microscopic examination of the specimen (Fig. 4) revealed leiomyoma.

Recovery was complicated by bronchitis and bronchopneumonia. There were at no time signs or symptoms of pleural or mediastinal infection. The intercostal drain was removed on the 3rd postoperative day and the sutures on the 10th day.

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The patient was fed parenterally for the first five postoperative days, after which time he was permitted to swallow small sips of water. On the 7th postoperative day soft food was allowed, and on the 10th postoperative day, solid food.

Esophagograms taken 3 weeks after the operation revealed a normal delineation of the esophagus, with some bulging in the area where the tumor was formerly located (Fig. 5). This may have been due to the absence of the intrinsic esophageal musculature although the patient had no difficulty in swallowing.



FIG. 1.—Large defect of the middle portion of the thoracic esophagus.

When seen 11 (eleven) months after operation the patient appeared to be in perfect condition. An esophagogram taken at this time was essentially the same as the previous one.

COMMENT. The choice of operation in this case was between esophagectomy and the plastic procedure described above. Allowing the denuded and poorly vascularized mucosa to remain without proper protection was hazardous because of the possibility of necrosis and perforation.

Esophagectomy was deemed inadvisable for the following reasons:

1. The risk of the operation would have been out of proportion to the benign character of the lesion.

2. Roentgen-ray pictures taken previous to the operation revealed a rather short stomach. It seemed questionable whether the entire length of the thoracic esophagus could be replaced by the mobilized stomach.

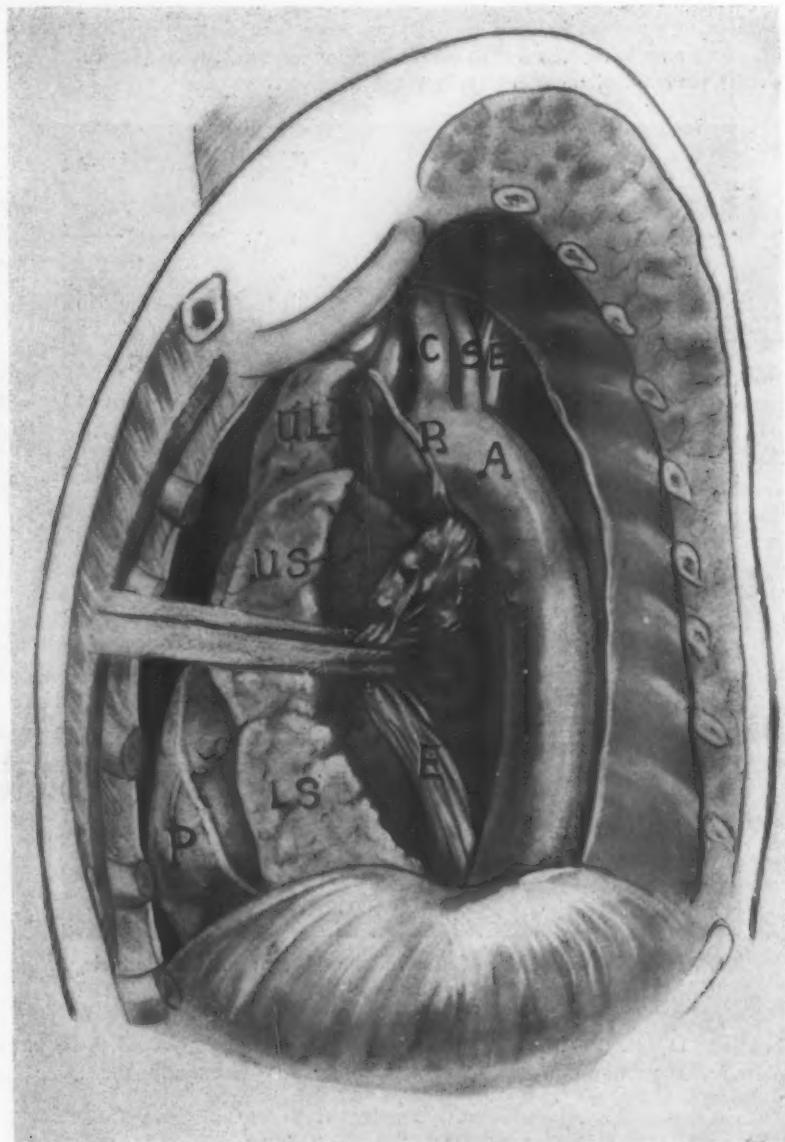


FIG. 2.—Sketch of the leiomyoma in situ.

A. Aorta	LS. Lower Segment of Lower Lobe
R. Recurrent Laryngeal Nerve	P. Pericardium with Phrenic Nerve
UL. Upper Lobe	E. Esophagus
US. Upper Segment of Lower Lobe	C. Arteria Carotis comm. sin.
	S. Arteria Subclavia sin.

3. Intrathoracic displacement of the partly devascularized and denervated stomach is followed by well known functional disorders. These may

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be disregarded in the presence of a carcinoma, but should be taken into account if removal of a benign lesion is planned.

In muscular or mucosal defects of the *lower* esophagus conditions are different. A pedicled flap taken from the diaphragm or a pedicled omental graft

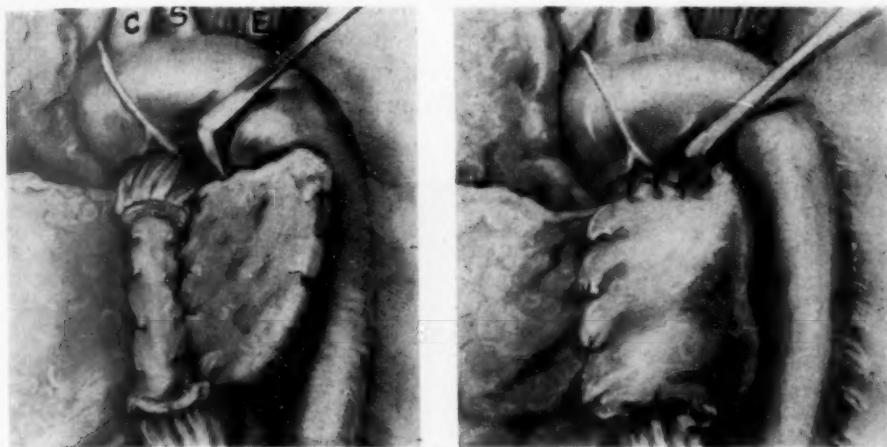


FIG. 3.—Sketch of the operative procedure. The denuded portion of the esophagus is covered by a pedicled flap of the upper segment of the lower lobe of the left lung.



FIG. 4.—Photography of the specimen.

brought into the thoracic cavity through a small transdiaphragmatic laparotomy can be used to reinforce the esophageal wall. Excision of the lower esophagus, which is less hazardous than total esophagectomy may be considered in these cases. However, out of three cases of resection of the lower

esophagus for myoma of the cardio-esophageal region (S. W. Harrington and H. J. Moersch,³ B. Dick⁷ and R. C. Brock¹), two died from pulmonary complications. Only Brock's case survived.

Simple excision of a leiomyoma of the lower esophagus was first performed by Sauerbruch⁵ in 1932. At operation an accidental tear was made into the mucosa. Since closure of this opening by two layers of sutures would have effected narrowing of the lumen, Sauerbruch made use of the opening in adding an esophagogastostomy. Additional cases of excision were reported

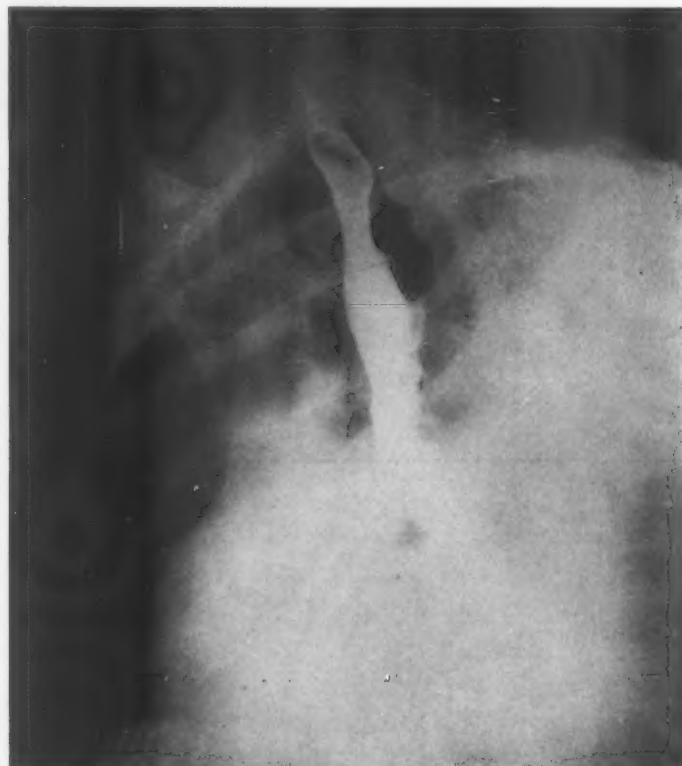


FIG. 5.—Esophagogram taken 3 weeks after the operation.

by T. Ohsawat⁴ in 1933 and by P. W. Schafer and C. F. Kittle⁶ in 1947. Schaefer and Kittle found it "necessary to excise an ovoid portion of the left posterolateral wall measuring 3 by 7 cm. This defect was closed longitudinally by two rows of interrupted O chromic catgut sutures." In these patients, where simple excision of leiomyoma of the lower esophagus was performed, recovery was uneventful.

Our case appears to be the first surgically treated leiomyoma of the middle portion of the esophagus.

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SUMMARY

An extensive muscular defect of the middle portion of the thoracic esophagus was covered by pedicled flap of lung tissue.

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RUPTURE OF A SUBPHRENIC ABSCESS INTO THE PERICARDIUM*

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DIRECT EXTENSION of a subphrenic abscess through a perforation in the diaphragm into the pleural cavity or lung is not uncommon, but a similar extension into the pericardial sac is apparently rare. The following case is presented because of its rarity and because it illustrates the occasional undesirable masking of deep seated suppurative processes by antibiotic and chemotherapeutic drugs.

CASE REPORT

First Admission: A. S., a 35-year-old, single white male was admitted to Kings County Hospital on October 9, 1946, with a ten-year story of symptoms compatible with gastro-duodenal ulceration and a recent sudden attack of severe epigastric pain. The clinical picture was that of a perforated peptic ulcer, and a celiotomy was performed 9 hours after the onset of symptoms. There were found a generalized acute peritonitis, a moderate amount of cloudy fluid in the abdominal cavity and a perforation 7 mm. in diameter on the anterior aspect of the first portion of the duodenum. An attached tab of lesser omental fat was placed into the perforation and held there with three silk sutures. The latter penetrated all layers of the bowel, which has been the usual method of closing large ulcers on this service. As much as possible of the free fluid was aspirated from the abdomen and the wound was closed without drainage.

The postoperative course was stormy and consisted of the following pertinent features: There was abdominal distention for the first 14 postoperative days. A rectal examination on the 12th day revealed a pelvic mass. A roentgenogram of the chest on the 28th postoperative day demonstrated a moderate pleural effusion at the left base and subillumination of the lower lung field on the right side. Four weeks later a second roentgenogram revealed almost complete resolution of the pleural effusion as previously observed. The temperature varied from 100° F to 101° F for the first 28 days, but had subsided to normal by the 33rd day and remained so thereafter.

In addition to the usual supportive measures the patient was given 3,520,000 units of penicillin during the first 12 days, and 4,800,000 units of penicillin and 132 Gm. of sulfadiazine from the 28th to the 48th postoperative day. The penicillin was given intramuscularly in doses from 30,000 to 50,000 units every 3 hours; and the sulfadiazine was administered by mouth, 1 Gm. every 4 hours. Fifty-one days after operation the white blood count was normal whereas it had been elevated during the period of pyrexia. At this time a rectal examination revealed the pelvic mass to have resolved into a small, non-tender, hard nodulation. On the 58th day following operation the patient was discharged to the Out-Patient Department feeling well. Subsequently, he was seen twice and complained of no symptoms relative to the ulcer, the operation or sequelae thereof.

Second Admission: The patient was readmitted to the hospital at 12:00 noon on January 30th, 1947, because of severe chest pain. Nine hours prior to admission he was awakened with a severe pain in the back at the level of the scapulae. The pain, which

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was slightly worse to the left of the midline, was steady and continuous. There was also noted a less severe, diffuse, sticking pain across the lower chest anteriorly. This was moderately exaggerated by deep respirations. Vomiting of clear fluid occurred several times. During the week prior to admission he had felt feverish, but there were no chills, and no abdominal pain.

Physical Examination: The patient was alert and cooperative, but acutely ill and apprehensive. There was moderate dilatation of the neck veins and a somewhat dusky red color to the skin of the upper chest and neck, but no pallor, cyanosis or jaundice were observed. The pulse rate was 144 per minute and regular. The respiratory rate was 36, temperature 105.8° F and the blood pressure was unobtainable. The findings pertaining to the lungs were not remarkable except for an area of increased whispered pectoriloquy and bronchial breathing in the right mid-chest posteriorly. This was not heard several hours later. The heart tones were normal but weak. The abdomen was flat, soft and not tender. The old operative scar was well healed, no masses were felt and the bowel sounds were normal. Digital rectal examination revealed the same findings as upon discharge, 8 weeks before. The white blood count was 12,000 with 66 per cent polymorphonuclear leukocytes.

A plain film of the abdomen demonstrated irregular distention of small bowel and some gas within the stomach. An upright two meter chest film revealed no evidence of recent pulmonary or pleural disease. There were, however, minimal thickening of the pleura at both apical regions and a few fibrotic deposits in the superior portion of the right hilum. There was no free air under the diaphragm. The cardiac contour was within normal limits.

General supportive and symptomatic treatment was instituted without beneficial response. Aspiration of the stomach yielded 500 cc. of light yellow fluid. During the afternoon the Trendelenburg position was instituted in an attempt to mitigate the vascular collapse, but it had to be discontinued because the clinical picture became even more alarming. The course was rapidly downhill and 8 hours after admission the pulse was no longer obtainable. Death occurred at 10:00 p.m., 10 hours after admission and 19 hours after the onset of symptoms.

Necropsy: Examination of the abdominal cavity revealed the spleen to be fixed in position by old fibrous adhesions and there were numerous intestinal adhesions, especially in the pelvis. There was no duodenal ulcer and the site of previous repair could not be identified by either gross cicatrix or the presence of sutures. To the left of the coronary and falciform ligaments, on the superior and anterior surface of the left lobe of the liver there was an abscess cavity which extended into and through a necrotic portion of the diaphragm. The cavity, which measured 2 cm. in diameter, had a thick fibrous wall. The abscess did not invade the liver substance nor did it communicate with the pleural sac. The abscess cavity was continuous, however, through a 2.5 mm. perforation in the diaphragm, with the pericardial sac. The latter contained about 350 cc. of grayish yellow pus and many recent fibrinous adhesions. The heart and great vessels were otherwise normal. Cultures of the pus from the abscess cavity grew hemolytic *staphylococcus aureus* and *escherichia coli*. Death was believed to have been caused by a fulminating suppurative pericarditis and cardiac tamponade.

COMMENT

In a limited review of the literature one other case of direct extension into the pericardium of a subphrenic abscess complicating a gastroduodenal perforation was found. Graves,¹ in 1863, described the perforation into the pericardial sac of an "hepatic" abscess, which was in direct continuity with the lumen of the stomach through a perforated gastric ulcer. Several cases of rupture of a gastric ulcer directly into the pericardium or heart itself have

been recorded.^{2, 3} Cabot⁴ reported one case of a pericardial perforation by a subphrenic abscess following biliary tract disease. Numerous writers have recorded isolated cases wherein an amoebic abscess of the liver extended into the subphrenic space and finally eroded through the diaphragm into the pericardial sac.^{5, 6, 7, 8, 9, 10} The latter condition is also discussed in various texts on tropical diseases.^{11, 12, 13} This complication is very rare, however, because it has always followed an abscess in the left hepatic lobe, which in itself is uncommon.¹³

In none of the reported cases reviewed, except those with pneumopericardium, was the diagnosis made clinically. To make this diagnosis Fontan¹³ has stated that one must have "an apprehensive patient complaining of left scapular, precordial and epigastric pain; decreased heart tones; a pericardial friction rub; and a sagacious observer." The clinical picture of acute pericarditis is not unlike that of myocardial infarction and the latter was considered in the differential diagnosis of the presented case. If one thinks of pericarditis however, the differential diagnosis can be made, as has been adequately discussed elsewhere.^{14, 15} When there are superimposed the signs of cardiac tamponade, *i.e.*, a "very weak heart," venous and capillary engorgement of the upper chest and neck, and aggravation of symptoms by the Trendelenburg position, the diagnosis should become apparent, especially in a patient with a history of antecedent subphrenic inflammation. When air is present in the pericardial sac the physical findings are unique. These have been recently discussed by H. Willy Meyer.¹⁶ In retrospect, it is believed that the diagnosis should have been strongly suspected in the presented case and that an exploratory pericardiotomy was indicated. Possibly this would have been life saving.

Another factor which may have altered the end result was the use of antibiotic and chemotherapeutic drugs in an attempt to control the infection during the first admission. Ochsner and Graves¹⁷ and Ochsner and DeBakey¹⁸ have stated that the majority of subphrenic "infections" subside spontaneously. Furthermore it has been postulated from bacteriologic studies,¹⁹ that the use of chemotherapy should reduce the mortality of gastroduodenal perforation. In this case, a subphrenic abscess was suspected on the 28th postoperative day. The seemingly satisfactory clinical response to penicillin and sulfadiazine masked the underlying suppurative process; therefore surgical exploration was no longer entertained. If these drugs had not been used the abscess probably would have been evacuated surgically, thereby obviating the lethal sequela. It is suggested that in the future one must continue to be watchful for occult abscesses even though the patient apparently responds well to chemotherapy, as evidenced by the usual clinical signs.

Thanks is expressed to Dr. Phillips F. Greene, Associate Dean, Long Island College of Medicine, for his aid in accumulating the bibliography.

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INTRAPAROTID SEBACEOUS GLANDS*

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THE ORIGIN OF MIXED TUMORS of the salivary glands has been disputed since the tumor was first described about 95 years ago. The term "mixed tumor" is based on the presence in such tumors of parenchymal tissues which are morphologically epithelial, and a chondromyxomatous stroma, the appearance of which indicates a mesodermal origin. Until fairly recently the controversy centered primarily in the conception that the tumors must arise in either one germ layer or the other—that they must be either mesothelial or epithelial in origin. One school advanced the theory that they might be endothelial in origin. Paget, Virchow, Billroth, Robin and others contributed to the literature of the subject in their time. More recently Ewing maintained that the tumors are derived from salivary epithelium which, retaining the power to secrete ptyalin and mucus, transforms the collagenous connective tissue stroma into mucoid tissue and finally into cartilage or pseudo-cartilage.¹ However, since new growths morphologically similar to mixed tumors of the salivary glands occur in the skin, mucous membranes, lungs, and in glands other than the salivary glands (such as the breast) the action of ptyalin and mucus secreting cells in producing them is not an entirely satisfactory explanation.

The various theories regarding these tumors have been summarized by Hemplemann and Womack² who have studied the tumors exhaustively by histochemical methods. Using technics first developed by Hemplemann they were able to demonstrate specific mesenchymal and epithelial mucoids or mucoproteins and conclude that both basic tissues contribute to the development of mixed tumors. Their work offers strong confirmation of this conception which has been expressed by many recent writers and they point out that "In line with embryologic evidence, the buccal ectoderm of the salivary gland anlage probably affects the surrounding buccal mesoderm. In turn, the differentiation and development of the ectoderm is probably influenced by the buccal mesoderm."

Ramsay,³ in discussing a constant epithelial rest known as the "Organ of Chievitz" arising in close relation to the embryonic parotid gland comments that "the ultimate fate of such an epithelial structure which becomes embedded in the surrounding tissue (mesenchyme) rests upon the early vascular and mechanical relations into which it is introduced. If favorable conditions are met in the developmental epoch of such an "inclusion" its fate might be quite different from that of a non-adaptive and passive existence."

A case recently seen in this Clinic is of some interest in this connection.

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CASE REPORT

The patient, B. H., was a 15-year-old boy who came to the Clinic December 27, 1947, complaining of an unsightly tumor on the left side of the face, just in front of the left ear. He had first observed it about a month previously. It had always been entirely painless and had grown very little since he first noticed it. He suffered from a rather severe acne vulgaris of the face, neck and shoulders and there was obvious overactivity of the sebaceous glands of his skin. He had thought that the lesion was a "wen" and paid little attention to it until it gradually became large enough to become unsightly.

Examination showed a hard, non-tender tumor 1.0 cm. in diameter about 2 cm.

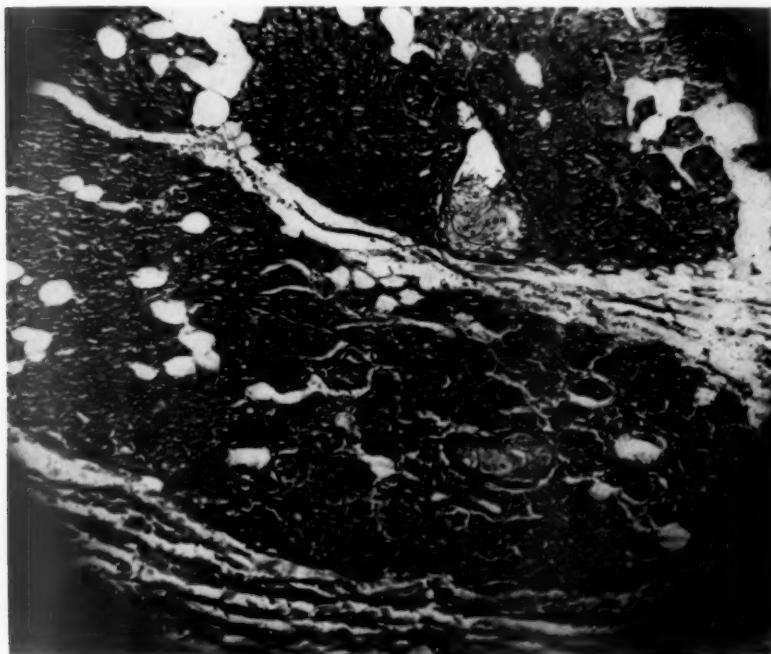


FIG. 1.—Photomicrograph of a section of the parotid gland showing well differentiated sebaceous glands within the parenchyma. These heterotopic glands were quite numerous, but rather widely scattered so that only two are seen in the illustration.

anterior to the tragus of the left ear. The skin was not adherent over any part of the lesion and palpation suggested that it lay in the parotid gland. There were numerous acne pustules and scars over the face and forehead and small sebaceous cysts about the ear.

The following day the tumor was removed under local anesthesia under a diagnosis of mixed tumor of the parotid gland. It was found to lie within the parenchyma of the gland, and although it was well encapsulated and was dissected out, a portion of the overlying parotid gland was removed with it. The wound healed uneventfully and the sutures were removed on the fourth postoperative day. There has been no recurrence to date (six months). Grossly the tumor was compatible with a mixed tumor. On microscopic examination, however, the main tumor mass proved to be the parotid lymph node in a state of hyperplasia. Interest centered in the fragment of parotid gland which had been removed with it. Scattered through the gland parenchyma were numerous heterotopic sebaceous glands (Figs. 1 and 2). These sebaceous glands were multiple and well differentiated and scattered diffusely through a considerable portion of the section. In

some the appearance of the glands suggested that they might be developing from intra-lobular ducts of the parotid gland, although this appearance might be attributed to the angle and level through which the section chanced to pass. There was a diffuse round cell infiltration of the parotid gland itself suggesting a chronic inflammatory process.

Only one comparable case has been discovered in a review of the available literature. This was reported by Hartz⁴ in 1946 and he had been unable to find a similar case in the literature up to that time. Ramsay⁵ states that the parotid anlage arises from the sulcus buccalis just back of the angle of the mouth after a certain amount of reduction in the oral cleft has taken place.

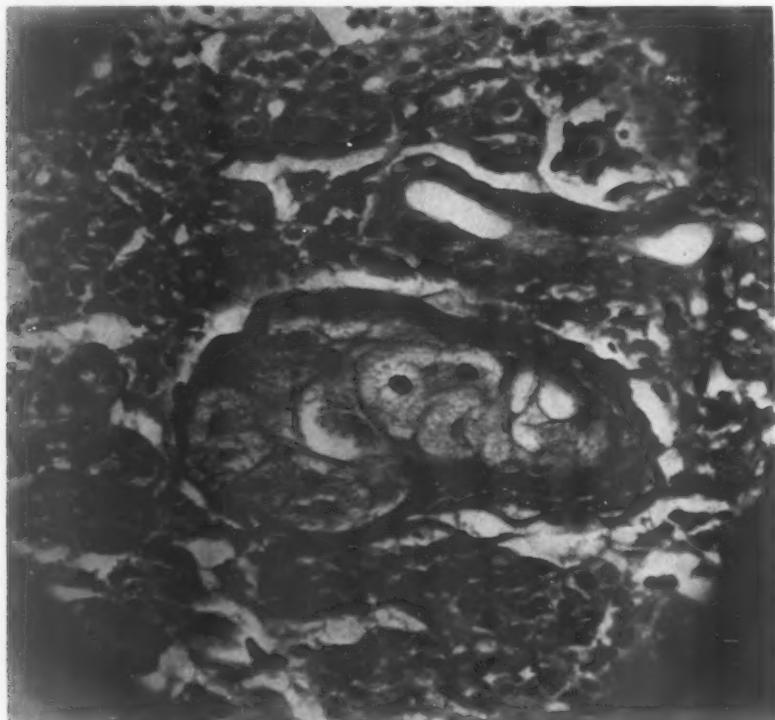


FIG. 2.—Higher magnification of one of the sebaceous glands seen in Figure 1.

giving opportunity for inclusion in the parotid bud of internally displaced epidermal material. For this reason the parotid gland would be expected to contain such elements as this case shows, in much greater frequency than would the organ of Chievitz since the latter arises from the buccal sulcus deeper (internally) than the parotid.

Moorhead,⁶ in presenting a series of mixed tumors of the skin, supports the now widely accepted view that mixed tumors arising in the skin, breast, salivary glands and other tissues are histogenetically similar. He believes⁷ that "mixed tumors—arise from pluripotential misplaced ectodermal cells which under proper conditions exert their property to differentiate into various structures normally derived from ectoderm." The connective tissue differen-

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tiations, that is the chondromyxomatous stroma, would correspondingly arise from the provocative action of abnormal connective tissue cells.

COMMENT

It would appear from the evidence here presented that well differentiated heterotopic holocrine glands probably appear in the otherwise normal salivary gland more often than would generally be suspected. That they have escaped attention is probably due to the fact that biopsy of the gland, except in cases of existing tumors is seldom indicated. If such is the case, the presence of these structures lends support to the opinion expressed by Moorhead that "mixed tumors of the skin, the salivary glands and the breast arise from abnormal epithelial cells which have similar developmental potentialities and which exert a provocative action on the mesoderm, resulting in the formation of heterotopic tissues of various types."

SUMMARY

A case is presented in which multiple well differentiated sebaceous glands are demonstrated within the parenchyma of the parotid gland.

The possible relationship of such structures to the origin of so-called "mixed tumors" is suggested.

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CERTAIN ANATOMIC FACTORS RELATED TO THE PATHOGENESIS OF HEMORRHOIDS*

THE AUTHOR'S "OBLITERATIVE SUTURE" IN THE TREATMENT OF THE
SMALL AND MIDDLE-SIZED INTERNAL HEMORRHOIDS*

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BY DEFINITION, hemorrhoids are venous dilatations or varices of the veins of the lower rectum and the anal canal. The appearance of this varicose condition seems to be closely related to the following six anatomic factors, existing in the anorectal region:

1. Absence of venous valves and lack of muscular or fascial support of the hemorrhoidal plexus.
2. Extreme looseness of the sub-mucous connective tissue rendering the effect of gravity particularly harmful in the sitting and standing postures. It is noteworthy that quadrupeds are almost free from hemorrhoids, as in them this region does not suffer from the results of gravity.
3. The passage of the tributaries of the superior hemorrhoidal vein directly through the muscular wall of the rectum (See Figs. No. 1 and 2) about $7\frac{1}{2}$ cm. above the anus, causing intermittent constriction of the veins at that point.
4. The communication of the superior hemorrhoidal vein (carrying most of the blood) with the inferior mesenteric vein, and thus with the portal system, which is subject to periodic physiologic congestion (as during digestion) and to frequent pathologic obstructions (liver cirrhosis, abdominal tumors, pregnancies, and other causes leading to portal hypertension).
5. The plexiform anastomoses just within the anus between the inferior and middle and the superior hemorrhoidal tributaries so that the former, although connected with the systemic circulation, are subject to dilatation as result of portal congestion.
6. The relation of the hemorrhoidal veins and of the terminal branches of the inferior mesenteric veins to the fecal contents of the sigmoid and rectum, exposing them to frequent pressure.

In evaluating the above six anatomic factors, one cannot help but attach most significance, as far as the pathogenesis of hemorrhoids from an anatomic point of view is concerned, to the lack of fascial support of the veins and to the looseness of the submucous connective tissue of the anorectal region.

The other factors follow closely, adding each one of them their weight to the appearance of the anal varicosities.

From the above, one may rightfully conclude that at least small and medium-sized internal hemorrhoids, especially the flat variety, could be treated effec-

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PATHOGENESIS OF HEMORRHOIDS

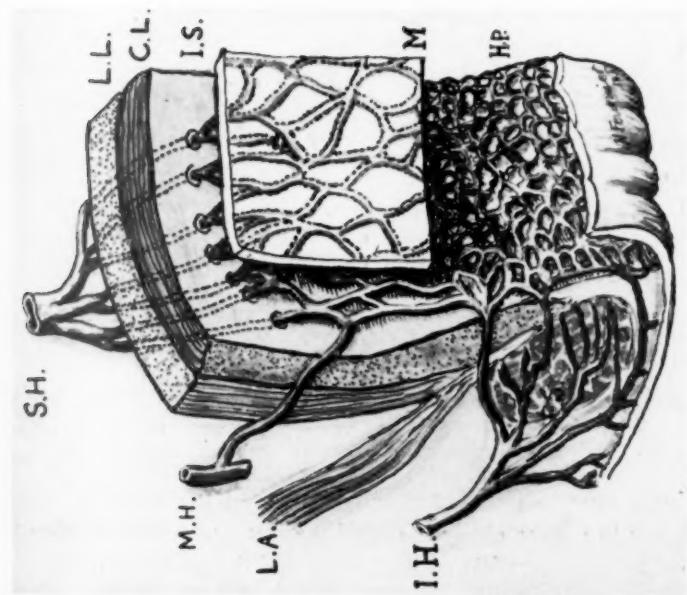


FIG. 1.—Schematic drawing showing: normal hemoroidal plexus (H.P.) formed by the anastomosis of the superior (S.H.), middle (M.H.), and inferior hemorrhoidal veins. The extreme looseness of the submucosa is represented by the distance between the mucosa (M) and the internal sphincter (I.S.).
L.A.—*Levator ani muscle*. LL—*Longitudinal muscular layer of the rectum*. CL—*Circular muscular layer*.
(Redrawn from F. Paitre, S. Dupret).

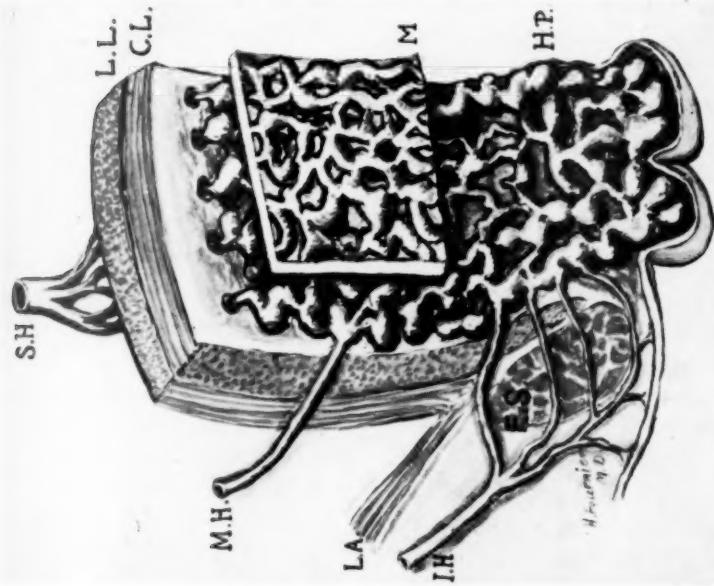


FIG. 2.—The anorectal region showing, as in Fig. 1, the formation of varicosities (interno-external hemorrhoids). Legend same as in Fig. 1.

tively by a continuous or interrupted "obliterative suture" (double o chromic catgut), which, embracing all the dilated veins (See Figs. No. 4 and 5), not only "obliterates" them but fixes them as well, through the production of dense connective tissue, to the rectal wall.

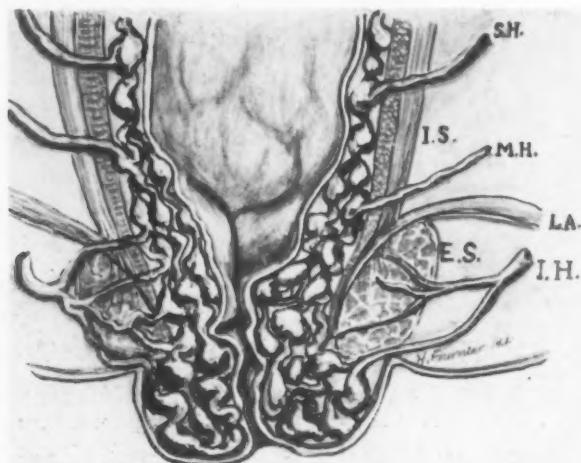


FIG. 3.—Frontal section of the rectum showing the development of hemorrhoids in an extremely loose submucosa. (Legends same as in Fig. 1.)

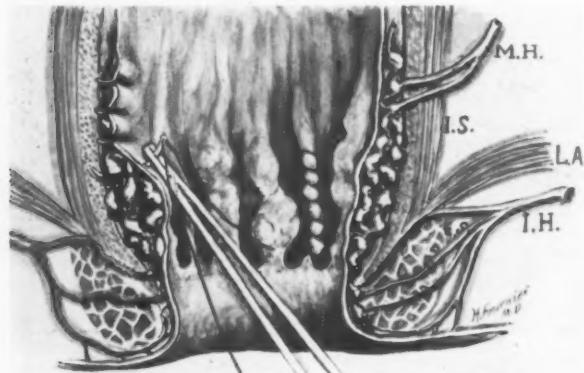


FIG. 4.—Frontal section of the rectum showing the application of the "Obliterative Suture" which at the same time is a fixative one. Note the simplicity of its application and the good results in collapsing the varicose veins and fixing the mucosa to the muscular layer.

This "obliterative suture" simplifies astonishingly the treatment of those hemorrhoids, which could not be easily clamped, excised, and ligated, due to their diminution during the dilatation of the rectum with rectal retractors.

Equally amenable to this treatment are those internal hemorrhoids that lie between excised and ligated masses where one hesitates to remove any more rectal mucosa for fear of undue trauma and hemorrhage.

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Figures 4 and 5 show in a semi-schematic way how the anorectal region would look after the application of this "obliterative suture."

TECHNIC

After the hemorrhoidal mass has been identified, one starts suturing its upper part (using an atraumatic curved needle, threaded with double 0 chromic catgut) transfixing its entire thickness by passing the needle from side to side.

In so doing, the needle should go deep enough to embrace slightly the muscular coat of the rectum so that, when one tightens the thread over the mass, the entire hemorrhoidal plexus of that area should be obliterated and fixed to the rectal wall.

After this first suture, which serves for anchorage, one proceeds to suture the entire mass in a continuous fashion, using the same needle threaded with

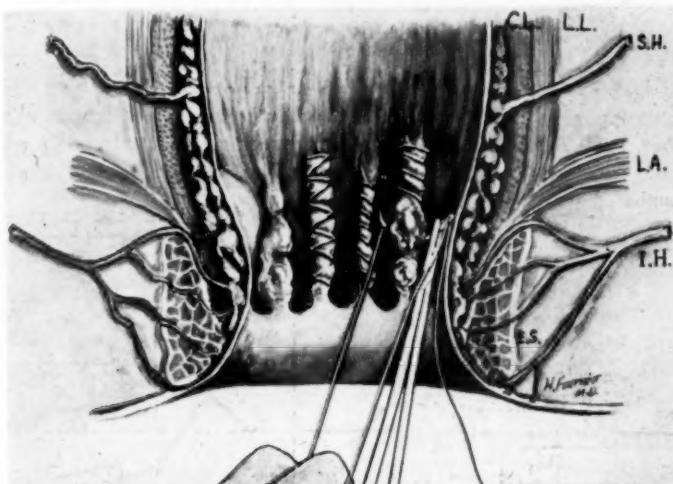


FIG. 5.—Showing the application of the "Obliterative Suture" in three hemorrhoidal masses. One hemorrhoid is still in process of being obliterated and fixed.

the same catgut. The needle should pass from side to side as was done in the beginning of the suture and the distance between the following ones (usually 3-4 mm) should be such as to allow a complete "obliteration" of the entire hemorrhoidal mass after tightening the thread (See Figs. 4 and 5).

One should end this continuous suture at this point, making a knot with the thread or if one wishes to add more secure "obliteration" one may continue in an ascending fashion to reach the starting point, where the thread is secured and its ends cut (See again Figs. 4 and 5).

SUMMARY

Certain anatomic factors have been mentioned which are related to the pathogenesis of anorectal varicosities and an "obliterative suture" has been proposed to deal with small and medium-sized internal hemorrhoids. This

suture is justified for the above-mentioned anatomical and pathologo-anatomic reasons.

The author is aware of the fact that for larger hemorrhoidal masses other well-known methods should be used (clamp-excision suture, clamp cautery, etc.). It is believed that this "obliterative suture" simplifies exceedingly the performance of a complete hemorrhoidectomy and renders this operation easier for the surgeon.

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CORRECTION

Through a typographical error in the article by Dr. John D. Stewart which appeared in the October, 1948, ANNALS OF SURGERY, we regret that Charts I and II were reversed. Of course, the legends are also incorrectly placed. Printed below are these two charts correctly numbered with the proper legend in each case.

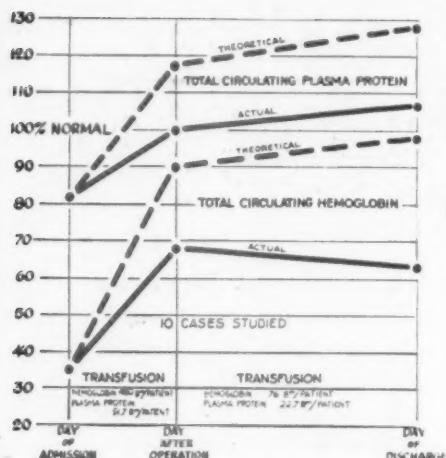


Chart I.—Study of effects of transfusion therapy on total circulating plasma protein and total circulating hemoglobin in 10 cases.

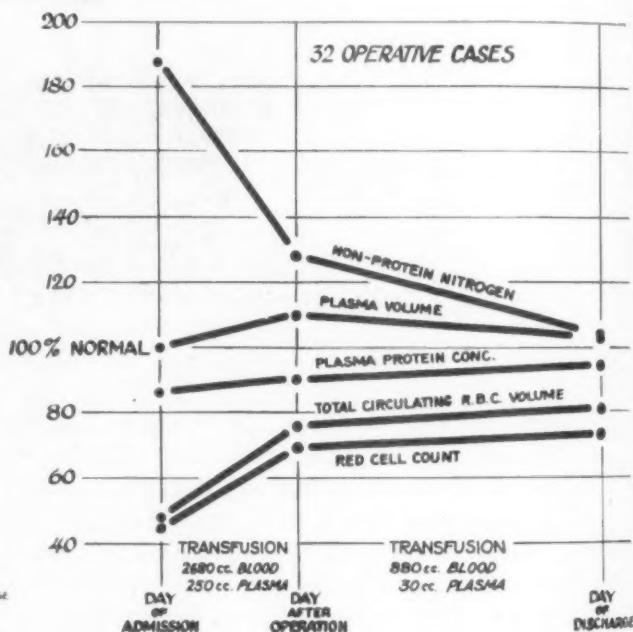


Chart II.—Average values for laboratory data in 32 operative cases of massively bleeding peptic ulcer.